23 Aggressive non-Hodgkin and Burkitt lymphoma

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Off-label drug use: Venetoclax in MCL; mogamolizumab in ATLL; ibrutinib, lenalidomide, mosenutuzumab, glofitamab, and epcoritomab in R/R DLBCL; and lenalidomide, ibrutinib, pomalidomide, and PD-1 inhibitors in R/R CNSL.

Aggressive B-cell lymphomas

Aggressive B-cell lymphomas are a heterogeneous group of neoplasms that arise from B cells in various stages of development. This group encompasses diffuse large B-cell lymphoma (DLBCL) and its variants, mantle cell lymphoma (MCL), Burkitt lymphoma (BL), and B-cell lymphoblastic lymphoma (Table 23-1). The unique histologic, cytogenetic, and molecular features of each subtype have therapeutic implications. These neoplasms are typically characterized by rapidly progressing nodal or extranodal disease and, although often potentially curable, are associated with relatively short survival in the absence of successful therapy. This chapter focuses on mature B- and T-/natural killer (NK)-cell neoplasms.

Diffuse large B-cell lymphoma

DLBCL is composed of large B cells with a diffuse growth pattern. The World Health Organization (WHO) classification recognizes several subcategories of DLBCL, including molecular subtypes (germinal center B cell [GCB], activated B cell [ABC], and unclassifiable); pathologic subtypes, including T-cell/histiocyte-rich large B-cell lymphoma; and defined disease entities, including primary mediastinal large B-cell lymphoma (PMBCL) and primary DLBCL of the central nervous system (CNS).

DLBCL constitutes approximately 30% of all Non Hodgkin Lymphomas (NHLs) and can present with nodal or extranodal disease. Bone marrow involvement with large-cell lymphoma occurs in 15% to 20% of cases. Another 10% to 20% of patients have discordant marrow involvement with a low-grade B-cell lymphoma, despite a nodal biopsy consistent with DLBCL.

In addition to the B-cell markers CD20 and CD19, the neoplastic cells may also express CD10 (30% to 60%), *BCL6* (60% to 90%), and IRF4/MUM1 (35% to 65%). Rare cases may express CD5 (10%) and must be distinguished from the blastoid variant of MCL, which is cyclin-D1-positive. As described, 2 molecularly distinct subtypes of DLBCL not otherwise specified (NOS) are recognized: GCB, which has a gene expression profile similar to germinal center B cells ($CD10^+$ and $BCL6^+$), and ABC, which has a profile similar to activated peripheral B cells ($IRF4/MUM^+$) with a prominent *NFkB* gene signature.

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Table 23-1 2016 World Health Organization classification of B-cell and T-cell neoplasms

B-cell neoplasms	T-cell neoplasms
Precursor B-cell neoplasms	**Precursor T-cell neoplasms**
B-lymphoblastic leukemia/lymphoma NOS	T-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	
Mature B-cell neoplasms	**Mature T-cell neoplasms**
Aggressive lymphomas	*Leukemic or disseminated*
Diffuse large B-cell lymphoma: variants, subgroups, and subtypes/entities	T-cell large granular lymphocytic leukemia Chronic lymphoproliferative disorders of NK cells T-cell prolymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell leukemia/lymphoma Systemic EBV-positive T-cell lymphoproliferative disorders of childhood
Diffuse large B-cell lymphoma, NOS Germinal center B-cell type Activated B-cell type	
Diffuse large B-cell lymphoma subtypes	*Extranodal*
T-cell/histiocyte-rich large B-cell lymphoma Primary DLBCL of the CNS Primary cutaneous DLBCL, leg type DLBCL associated with chronic inflammation HHV-8–positive DLBCL, NOS EBV-positive DLBCL, NOS	Extranodal NK/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Monomorphic epitheliotropic intestinal T-cell lymphoma Hepatosplenic T-cell lymphoma Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract Breast implant-associated anaplastic large-cell lymphoma
Other lymphomas of large B cells	*Cutaneous*
Primary mediastinal large B-cell lymphoma Intravascular large B-cell lymphoma EBV-positive mucocutaneous ulcer Lymphomatoid granulomatosis ALK-positive large B-cell lymphoma Plasmablastic lymphoma Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease Primary effusion lymphoma	Mycosis fungoides Sézary syndrome Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorder Primary cutaneous $CD4^+$ small/medium T-cell lymphoma Primary cutaneous acral $CD8^+$ T-cell lymphoma Primary cutaneous anaplastic large-cell lymphoma Lymphomatoid papulosis Subcutaneous panniculitis-like T-cell lymphoma Primary cutaneous γδ T-cell lymphoma Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma Hydroa vacciniforme-like lymphoma
	Nodal
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	Peripheral T-cell lymphoma, NOS Angioimmunoblastic T-cell lymphoma Follicular T-cell lymphoma Nodal peripheral T-cell lymphoma with TFH phenotype Anaplastic large-cell lymphoma, ALK positive Anaplastic large-cell lymphoma, ALK negative
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	
High-grade B-cell lymphoma, NOS	
Burkitt lymphoma	
Burkitt-like lymphoma with 11q aberration	
Mantle cell lymphoma	
In situ mantle cell neoplasia	
Indolent lymphomas	
Follicular lymphoma In situ follicular neoplasia Duodenal-type follicular lymphoma Testicular follicular lymphoma Pediatric-type follicular lymphoma Large B-cell lymphoma with *IRF4* rearrangement Primary cutaneous follicle center lymphoma	

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Table 23-1 2016 World Health Organization classification of B-cell and T-cell neoplasms *(continued)*

B-cell neoplasms	T-cell neoplasms
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)	
Nodal marginal zone lymphoma	
Splenic marginal zone lymphoma	
Splenic B-cell lymphoma/leukemia, unclassifiable	
Lymphoplasmacytic lymphoma	
Heavy chain disease	
Plasma cell neoplasms	
CLL/SLL	
Monoclonal B-cell lymphocytosis	
B-cell prolymphocytic leukemia	
Hairy cell leukemia	

CLINICAL CASE

A 52-year-old man is diagnosed with stage IVB DLBCL. On positron emission tomography–computed tomography (PET-CT) imaging, the largest nodal mass was 6 cm in the retroperitoneal region, and there was lymphoma involvement of liver and bone. Laboratory studies show a normal complete blood count and normal chemistries, aside from lactate dehydrogenase (LDH) elevated 1.5 times normal. His Eastern Cooperative Oncology Group performance status (ECOG PS) was 1. Immunophenotypic stains of the lymphoma cells revealed expression of CD19, CD20, κ light chain, *BCL2*, *MYC*, and MUM1/IRF4. Lymphoma cells were negative for CD10 and *BCL6* expression. Fluorescence in situ hybridization (FISH) was negative for *MYC* rearrangement.

Clinical prognostic factors in DLBCL

Approximately 2/3 of patients diagnosed with DLBCL can be cured with rituximab-based chemotherapy; however, low- and high-risk groups can further be defined by clinical and biological factors. Although the International Prognostic Index (IPI) is robust and relevant in the modern rituximab treatment era, it does not capture all prognostic information. The patient described in the clinical case has an IPI score of 3 (advanced-stage, multiple sites of extranodal involvement, elevated LDH), placing him in a high-intermediate-risk group with an expected 5-year probability of survival with Rituximab-Cyclophosphamide, Doxorubicine, Vincristine and Prednisone (R-CHOP) of 50% to 60%.

Biological prognostic factors in DLBCL

Although the IPI is easy to apply and remains valid in the current treatment era, it fails to capture underlying biological heterogeneity. As described previously, DLBCL can be divided molecularly by gene expression profiling (GEP) into the GCB and ABC subtypes, which also have a signature distinct from PMBCL. ABC-DLBCL has an inferior prognosis, independent of the IPI. The use of GEP has had limited clinical utility because of its long turnaround time, the need to use fresh frozen tissue, technical complexity, and lack of routine availability in the clinic.

Immunohistochemical (IHC) algorithms have been used to capture the cell-of-origin (COO) phenotype using a methodology that can be applied routinely in clinical practice. Hans et al. first reported an IHC algorithm to distinguish the GCB versus non-GCB subgroups using CD10, *BCL6*, and IRF4/MUM1. Using the complementary DNA microarray as the gold standard, the sensitivity of the IHC COO subgrouping was 71% for the GCB group and 88% for the non-GCB group. Other algorithms have been proposed that also have a lower sensitivity than gene expression profiling. These results, however, have been inconsistent as to whether the COO distinction by IHC can be applied to rituximab-treated patients. One study found that none of the applied 5 different IHC algorithms could distinguish COO subgroups with prognostic significance. Given the lack of data suggesting that alternate therapies may affect outcome, the COO information, whether by molecular profiling or immunohistochemistry, should not be used to direct treatment decisions outside of clinical trials.

Recent technological advances in GEP, allows real-time COO determination from formalin-fixed paraffin-embedded tissue (FFPET). The Lymphoma/Leukemia Molecular Profiling Project developed the Lymph2Cx assay, a parsimonious digital gene-expression (NanoString)–based test for COO assignment in FFPET. A 20-gene assay was trained using 51 FFPET biopsies, and the locked assay was subsequently validated using an independent cohort of 68 FFPET biopsies. Comparisons were made with COO assignment using the original COO model on matched frozen tissue. The assay was highly accurate; only 1 case with definitive COO was incorrectly assigned with >95% concordance of COO

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assignment between 2 independent laboratories. The test turnaround time is several days, making Lymph2Cx attractive for implementation in clinical trials and practice. However, until gene expression analysis becomes clinically available, the 2016 WHO classification includes subclassification of DLBCL NOS as GCB or non-GCB based on IHC algorithms.

High-grade B-cell lymphoma not otherwise specified (HGBCL-NOS) may be associated with poor prognosis following standard R-CHOP chemotherapy based on the identification of a molecularly high-grade subset and a significant proportion of HGBCL found to have a "double-hit signature" molecularly without expected rearrangements in *MYC/BCL2*.

MYC is translocated in ~10% of DLBCLs, and early studies have suggested that *MYC* is associated with an aggressive course in the pre- and post–rituximab treatment eras. In some cases, there is also a t(14;18) involving *BCL2,* or a *BCL6* translocation involving chromosome 3, termed *double-hit lymphoma* (DHL) or *triple-hit lymphoma* (THL), if all 3 translocations are present. DHL/THL can occur as a high-grade transformation from an underlying FL or as a de novo disease. The combination of *MYC* driving cellular proliferation and *BCL2* preventing apoptosis has proven to be an extremely high-risk biologic subset of aggressive lymphomas with low cure rates using traditional R-CHOP. In the 2016 WHO, DHL is now a distinct molecularly defined aggressive lymphoma called *high-grade B-cell lymphoma with* MYC *and* BCL2 *and/or* BCL6 *rearrangements*. With the recent availability of a *MYC* antibody for IHC analysis, 2 large-scale studies have evaluated the prognostic importance of *MYC* and *BCL2* protein expression (double expressers) in DLBCL patients treated with R-CHOP chemotherapy. *MYC* protein expression was found in approximately 1/3 of cases, a higher incidence than that captured by FISH analysis (11%) or high *MYC* mRNA expression, suggesting that multiple roads of *MYC*-deregulation exist. Importantly, the double expressers, which account for 30% of newly diagnosed DLBCLs, have an inferior prognosis relative to other DLBCLs, though not as poor as for patients with DHL. Novel treatment approaches for these high-risk patients are needed.

Treatment of newly diagnosed DLBCL

Advanced-stage DLBCL

The backbone treatment of all subtypes of DLBCL is anthracycline-based treatment with R-CHOP chemotherapy. With this approach, approximately two thirds of patients are cured.

Rituximab has several mechanisms of action, including the ability to sensitize otherwise-resistant lymphoma cells to chemotherapy agents in vitro, perhaps, in part, via downregulation of the BCL-2 protein. Groupe d'Etude des Lymphomes de l'Adulte (GELA) published a landmark phase 3 clinical trial in which 399 patients 60 to 80 years of age with previously untreated advanced-stage $CD20^+$ DLBCL were randomized to receive CHOP for 8 cycles or R-CHOP on a standard 21-day schedule. R-CHOP demonstrated an improvement over CHOP for all endpoints, including complete response (CR) rate, event-free survival (EFS), and overall survival (OS). With longer follow-up, the results held, and R-CHOP quickly became the standard of care for advanced-stage DLBCL globally (Table 23-2). More recently, the median 10-year-outcome of patients in this study demonstrated a 10-year progression-free survival (PFS) for R-CHOP-treated patients of 35% (versus 20% for CHOP alone) and a 10-year overall survival of 43.5% (versus 27.6% for CHOP alone) (Table 23-2). A similar phase 3 study was carried out by the United States (US) ECOG intergroup (E4494 study) comparing 6 to 8 cycles of CHOP versus R-CHOP in elderly patients with aggressive lymphoma, which included a second randomization in CR patients comparing observation and rituximab maintenance therapy every 6 months for 2 years. Unlike the GELA study, there was no response rate or OS difference detected, although there was a benefit in time to treatment failure for the R-CHOP arm. The analysis was confounded to some extent by the secondary randomization to maintenance versus no-maintenance rituximab. Maintenance therapy was beneficial for the time to treatment failure only in the CHOP-induction subset. As such, interpretation of these results supports the use of R-CHOP induction without subsequent maintenance rituximab therapy.

Two other randomized controlled studies have been published supporting the benefit of the addition of rituximab to anthracycline-based chemotherapy in DLBCL. The MabThera International Study Group (MInT) study included young (<60 years old), low-risk (age adjusted International Prognostic Index [aaIPI] 0 or 1) patients with DLBCL (including PMBCL) who primarily received CHOP or CHOP plus etoposide (CHOEP) with or without rituximab. The rituximab-containing regimens demonstrated an improvement in EFS and OS (Table 23-2). The Rituximab with CHOP Over age 60 Years (RICOVER-60) trial by the same group evaluated CHOP-14 (every 14 days) for 6 or 8 cycles, with or without rituximab in elderly patients and demonstrated a significant improvement in all endpoints with the rituximab combinations. Of note, the latter study also established that 6 cycles of R-CHOP-14 was associated with the best outcome.

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Table 23-2 Key trials of diffuse large B-cell lymphoma using rituximab-containing regimens

Authors (trial/phase)	*N*	Treatment	Patient selection	PFS/EFS	OS
Coiffier et al, *N Engl J Med*. 2002 (GELA/phase 3)	202	R-CHOP × 8	Age 60-80 y Stage II-IV	57% vs 38% (2 y)	70% vs 57% (2 y)
	197	CHOP × 8			
Pfreundschuh et al, *Lancet Oncol*. 2006 (MInT/phase 3)	413	R-CHOP-like‡ × 6	Age 18-60 y aaIPI 0 or 1 Stage I (+bulk or II-IV)	74% vs 56% (6 y)	90% vs 80% (6 y)
	410	CHOP-like‡ × 6			
Pfreundschuh et al, *Lancet Oncol*. 2008 (RiCOV-ER-60/phase 3)†	306	R-CHOP-14 × 6	Age 61-80 y Stage I-IV	66.5% (3 y) 63% (3 y)	78% (3 y) 72.5% (3 y)
	304	R-CHOP-14 × 8			
	209	CHOP-14 × 6		47% (3 y) 53% (3 y)	68% (3 y) 66% (3 y)
	219	CHOP-14 × 8			
Cunningham et al, *Lancet*. 2013 (NCRI/phase 3)	540	R-CHOP-21 × 8	Age 61-80 y	81% vs 83% (2 y)★	81% vs 83% (2 y)★
	540	R-CHOP-14 × 6 + G-CSF			
Delarue et al, *Lancet Oncol*. 2013 (LNH03-6B/phase 3)	296	R-CHOP-21 × 8	Age 60-80 y aaIPI > 1	60% vs 56% (3 y)★	72% vs 69% (3 y)★
	304	R-CHOP-14 × 6			
Recher et al, *Lancet*. 2011 (LNH03-2B/phase 3)	196	R-ACVBP	Age 18-59 y aaIPI 1	87% vs 73% (3 y)	92% vs 89% (3 y)
	183	R-CHOP			
Bartlett et al, *J Clin Oncol*. 2019 (CALGB 50303/ phase 3)	250	R-CHOP × 6	18 y + Stage II-IV	78.9% DA-R-EP-OCH vs 75.5% (2y)	86.5% DA-R-EP-OCH vs 85.7% (2y)
	241	DA-R-EPOCH × 6			
Younes et al, *J Clin Oncol*. 2019 (phase 3)	419	R-CHOP × 6	18 y + Non-GCB by Hans algorithm Stage II-IV	**EFS** <60 yo 75.4% R-CHOP + ibrutinib vs 64.6% (3y) >60 yo 66% R-CHOP + ibrutinib vs 69.6% (3 y) **PFS** <60 yo 77.4% R-CHOP + ibrutinib vs 66.3% (3 y) >60 yo 66.8% R-CHOP + ibrutinib vs 69.6% (3 y)	<60 yo 93.2% R-CHOP + ibrutinib vs 80.9% (3 y) >60 yo 76.6% R-CHOP + ibrutinib vs 81.7% (3 y)
	419	R-CHOP + ibrutinib × 6			
Nowakowski et al, *J Clin Oncol*. 2021 (ROBUST/ phase 3)	285	R-CHOP × 6	18-80 yo ABC subtype by Nanostring Stage II-IV	67% R-CHOP + lenalidomide vs 64% (2 y)	79% R-CHOP + lenalidomide vs 80% (est. 2 y)
	285	R-CHOP + lenalidomide × 6			
Nowakowski et al, *J Clin Oncol*. 2021 (E1412/phase 2)	171	R-CHOP × 6	18 y + Stage II-IV	76% R-CHOP + lenalidomide vs 62% (3 y)	83% R-CHOP + lenalidomide vs 75% (3 y)
	166	R-CHOP + lenalidomide × 6			

Survival estimates shown for rituximab-containing regimens only and are rounded off where applicable to the nearest whole number.

est., estimated; NCRI, British National Cancer Research Institute Study; R, rituximab; yo, years old.

‡87% DLBCL; CHOP-like = CHOP-21 or CHOEP-21 in 92%; radiotherapy given to sites of bulk, extranodal disease (physician's discretion).

†80% DLBCL.

★*P* value not significant (all other *P* values for comparisons are significant).

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Two randomized studies (GELA LNH03-6B and the British National Cancer Research Institute) compared R-CHOP-21 (every 21 days) with R-CHOP-14 (every 14 days), and there was no improvement of failure-free survival (FFS) or OS using the shortened cycle interval, thus establishing R-CHOP-21 as the standard (Table 23-2). Based upon the observations that older women fare better with R-CHOP than do older men, and that older men clear rituximab more rapidly, dose-dense rituximab was tested in a phase 3 study (HOVON-84), but there was no difference in the rate of complete response following R-CHOP induction. A trial where older men were treated with a higher dose of rituximab given at 500 mg/m^2 while women received the standard dose of 375 mg/m^2 showed that outcomes for male patients treated with higher-dose rituximab were equivalent to outcomes of female patients treated with the standard dose. Several recent randomized trials have sought to improve upon R-CHOP results in DLBCL. Explored strategies compared to standard R-CHOP have included substituting the next generation anti-CD20 monoclonal antibody obinutuzumab for rituximab; addition of bortezomib, lenalidomide, or ibrutinib; maintenance everolimus; consolidation with high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT); and infusional therapy with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R). No randomized trial has shown improvement in survival over standard R-CHOP. As a result, R-CHOP every 21 days for 6 cycles remains the standard of care for advanced-stage DLBCL.

Treatment of limited-stage DLBCL

Approximately 45% of cases of DLBCL are limited-stage (Ann Arbor stages I and II). A large randomized Southwest Oncology Group (SWOG) trial (SWOG-8736) in the pre-rituximab era established that combined modality therapy (CMT), including chemotherapy followed by radiation therapy (RT), was superior to CHOP alone for localized [stage I(E), nonbulky stage II(E)] aggressive lymphoma. In this study, the 5-year PFS (77% versus 65%, $P = 0.03$) and OS (82% versus 72%, $P = 0.02$) for 3 cycles of CHOP followed by involved-field radiation therapy (IFRT) was superior to that of 8 cycles of CHOP alone. An update of the study with longer follow-up, however, showed that the treatment advantage for the CMT was not sustained: there was an identical 10-year PFS of 55% in both treatment arms.

The benefit of rituximab has not been specifically analyzed in a randomized controlled trial in localized DLBCL. Most patients in the MInT study had limited-stage disease by nature of the inclusion criteria, and that study confirmed the benefit of rituximab in this population. The SWOG completed a phase 2 study evaluating 3 cycles of R-CHOP, with 4 doses of rituximab, followed by IFRT (40-46 Gy, if CR, and 50-55 Gy, if partial response [PR]) in patients with localized aggressive B-cell lymphoma, most of whom had DLBCL. Patients had to have at least 1 risk factor by the stage-modified IPI and had a 10-year PFS and OS of 58% and 67%, respectively.

With potential acute and more concerning long-term side effects of radiotherapy, determining whether a subgroup of patients with limited-stage DLBCL can be selected to receive chemotherapy alone is an important issue. A French study in limited-stage nonbulky (<7 cm) DLBCL randomized patients to 4 to 6 cycles of R-CHOP followed by 40 Gy RT or to 4 to 6 cycles of R-CHOP alone. Patients with an IPI score of 0 received 4 cycles, while patients with IPI scores ≥1 received 6 cycles. Only patients in a CR by PET-CT were randomized between chemotherapy alone or CMT, while all PR patients received CMT. Eighty-eight percent of patients achieved a CR and were randomized, with no difference in 5-year EFS or OS between the treatment arms. These data validate chemoimmunotherapy alone as an appropriate treatment plan for nonbulky limited-stage DLBCL patients who achieve a CR to R-CHOP.

In an National Clinical Trial Network study, 128 patients with early-stage nonbulky (<10 cm) disease received R-CHOP × 3 followed by an interim PET for response assessment. If PET-negative, patients received a fourth cycle of R-CHOP; if PET-positive, they received IFRT and radioimmunotherapy (only 11%). This study established R-CHOP × 4 as a suitable option for patients with early-stage DLBCL who achieve an interim negative PET.

Primary testicular DLBCL represents a unique subset of DLBCL, most commonly presenting with limited stage. These patients have a propensity for late relapse, as well as a high risk of CNS recurrence (parenchymal > leptomeningeal) and recurrence within the contralateral testis. As such, patients with primary testicular DLBCL are typically treated with 6 cycles of R-CHOP, including CNS prophylaxis, followed by prophylactic scrotal radiation to the contralateral testis.

Novel strategies to improve cure rates in DLBCL

Although the outcome of DLBCL has improved with R-CHOP chemotherapy, ~43% of patients still relapse after primary therapy, and most relapsing patients will not be cured of their disease. As noted previously, multiple randomized trials have failed to identify therapy superior to R-CHOP. Ongoing trials are now seeking to incorporate novel target agents with a biologic rationale in discrete DLBCL subsets. Both lenalidomide and ibrutinib may be

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selectively beneficial in ABC-DLBCL, with each showing single-agent activity in relapsed ABC-DLBCL compared to GCB. Randomized trials comparing R-CHOP to R-CHOP plus lenalidomide and R-CHOP to R-CHOP plus ibrutinib specifically looking at the ABC subtype have been completed and unfortunately did not show a strong advantage over R-CHOP alone though selection bias may have impacted results to some degree. The exception may be an OS advantage seen in patients younger than 60 years of age with R-CHOP plus ibrutinib.

Management of relapsed and refractory DLBCL

Repeating a biopsy at the time of suspected recurrence is recommended given the implications of recurrent DLBCL and possibility of relapse with a different histology. Following confirmation of recurrence, patients should undergo full restaging investigations. If the patient does not have significant comorbidities and is younger than 70 years of age, second-line (salvage) combination chemotherapy such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-DHAP (rituximab, dexamethasone, cytarabine [Ara-C], cisplatin), or R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) should be given, followed by HDC/ASCT if chemotherapy-sensitive disease is demonstrated. The evidence supporting the use of HDC/ASCT in relapsed DLBCL is based on the historic Parma study (named after the city of Parma, Italy where the study group who conducted the trial first met). Patients, who relapsed with aggressive lymphoma (excluding CNS or bone marrow involvement) following an initial CR to primary therapy, received 2 cycles of DHAP chemotherapy. If chemosensitivity (ie, a PR or CR to salvage chemotherapy) was demonstrated, patients were then randomized to receive further chemotherapy with DHAP or with HDC with BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) and ASCT. Patients in the transplantation arm had an improvement in both the 5-year EFS (46% versus 12%, $P = 0.001$) and OS (53% versus 32%, $P = 0.038$). Randomized trials in the modern era, however, have demonstrated disappointing success rates with this approach in patients who relapse or are refractory to R-CHOP, with fewer than 30% of patients remaining progression-free at 2 years.

The optimal salvage therapy has recently been investigated in 3 phase 3 randomized controlled trials. The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study randomized patients with relapsed DLBCL (or those who had not achieved a CR) to receive R-DHAP for 3 cycles followed by HDC with carmustine, etoposide, cytarabine and melphalan (BEAM)/ASCT if a response was demonstrated. There was also a second randomization following transplantation to rituximab or to observation to evaluate the role of maintenance therapy. At diagnosis, 62% of the patients had been treated with a CHOP-like regimen with rituximab. The overall response rate (ORR) was similar between R-DHAP and R-ICE (63% versus 63.5%), and there was no difference in EFS or OS, and maintenance rituximab did not affect outcome. Patients who previously received rituximab with their primary therapy had an inferior response rate (51% versus 83%, $P < 0.001$) and an inferior 3-year EFS (21% versus 47%), suggesting that these patients represent a very chemoresistant group. Additional poor prognostic factors that emerged from this study were early relapse <1 year and an aaIPI of 2 or 3. Interestingly, a subsequent correlative study suggested that patients with GCB DLBCL had an improved outcome to R-DHAP compared with R-ICE (3-year PFS 52% versus 32%, $P = 0.018$), which was even more striking if cases were defined by GEP (3-year PFS 100 % versus 27%), but the numbers were small. A second phase 3 trial was conducted by the National Cancer Institute of Canada comparing R-DHAP to the outpatient salvage regimen R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) in aggressive lymphomas using a noninferiority design. The ORR, EFS, and OS were similar between the treatment arms, but the R-GDP arm was associated with less grade 3 or 4 toxicity ($P = 0.0003$), including febrile neutropenia (9% versus 23%, $P < 0.0001$); patients had superior quality of life scores. Finally, a third randomized trial evaluated ofatumumab-DHAP versus R-DHAP as salvage therapy prior to ASCT in relapsed DLBCL and found no difference between the arms. The complete response rates to salvage therapy were low in both arms, and only 25% of patients remained progression-free at 2 years, highlighting treatment of relapsed DLBCL as a largely unmet medical need in the modern era. The primary predictor of success was achieving a CR by PET scan prior to ASCT.

Management of non-transplant-eligible patients with relapsed or refractory DLBCL, including novel therapies

Many patients relapse after HDC/ASCT or are not eligible for curative-intent treatment with salvage chemotherapy and HDC/ASCT because of advanced age or comorbidities. The goal of treatment in this setting is typically palliative; therefore, lower intensity regimens are typically employed which may offer short-term disease control with modest treatment-associated toxicity. Commonly used regimens in this context include gemcitabine-based regimens, such as R-GemOx (rituximab, gemcitabine, oxaliplatin), or bendamustine-rituximab (BR). Certain

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Table 23-3 Novel agents approved for R/R DLBCL

Therapy	Drug class	Patient population	Outcomes
Tafasitamab (with lenalidomide) L-MIND study	Fc-Enhanced ant-CD19 monoclonal antibody	R/R DLBCL not eligible for HDT/ASCT	ORR 60% CR 43%
Polatuzumab vedotin (with BR or BG*)	Anti-CD79b antibody drug conjugate	R/R DLBCL not eligible for HDT/ASCT	CR 40% Pola-BR (vs 17% BR alone)
Loncastuximab tesirine	Anti-CD19 antibody drug conjugate	R/R DLBCL after ≥2 lines of therapy	ORR 48% CR 24%
Selinexor	Selective inhibitor of nuclear export	R/R DLBCL after ≥2 lines of therapy and not eligible for HDT/ASCT	ORR 28% CR 12%

*obinutuzumab

therapies may also be appealing in selected subsets of relapsed/refractory (R/R) DLBCL. For tumors expressing CD30, the anti-CD30 antibody drug conjugate brentuximab vedotin produces an ORR of 44% with a median duration of response (DOR) of approximately 6 months and should be considered as an option in relapsed/refractory $CD30^+$ DLBCL. Lenalidomide monotherapy produces responses in approximately 1/4 of relapsed DLBCL patients, but the response rate and durability represent the subset of patients with non-GCB DLBCL for whom this therapy should be considered. Similarly, the Bruton tyrosine kinase inhibitor (BTKi) ibrutinib produces selectively higher responses in the ABC subset of DLBCL in whom the ORR was 37%. Interestingly, the pattern of mutations within the ABC-DLBCL may help predict patients more likely to respond to ibrutinib. Patients harboring mutations of both *CD79B* and *MYD88* appear to have the highest likelihood of response, while *CARD11* and *TNFAIP3* mutations appear unlikely to respond.

Most recently, genetically modified autologous chimeric antigen receptor (CAR) T cells targeting CD19 have emerged as highly active agents in the management of chemotherapy-refractory DLBCL. There are now 3 United States Food and Drug Administration (FDA)–approved anti-CD19 CAR T-cell products approved for R/R aggressive B-cell DLBCL that has failed at least 2 prior lines of therapy: axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel, which have ORRs ranging from 52% to 82% (40% to 54% CR). Additional details regarding CAR T-cell therapy are discussed in Chapter 14. Toxicities from CAR T cells include cytopenias resulting from the lymphodepleting chemotherapy as well as cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome.

Several novel agents have been approved recently for non-transplant-eligible patients with relapsed/refractory DLBCL (Table 23-3).

Results from ongoing studies evaluating several bispecific antibodies (mosenutuzumab, glofitamab, and epcoritomab) in relapsed and refractory DLBCL are encouraging with responses seen even in patients who have failed CAR T therapy.

Special situations: management of specific clinicopathologic entities of DLBCL

Primary mediastinal (thymic) large B-cell lymphoma

PMBCL was recognized as a specific entity in the WHO classification based on unique clinicopathologic presentation. Unlike typical cases of DLBCL, PMBCL occurs at a median age of 35 years and is slightly more common in women than in men. Most patients present with a bulky anterior mediastinal mass that can invade the lung and chest wall and can occasionally cause superior vena cava syndrome. Distant spread is uncommon at diagnosis, occurring in about 1/4 of patients. At relapse, involvement of visceral extranodal sites, including the kidneys, adrenals, ovaries, liver, and CNS, can occur.

Histologically, sclerosis is typically present, and phenotypically, the cells lack surface immunoglobulin expression but express B-cell markers such as CD19 and CD20. CD30 expression is present in 80% of cases; however, it is usually weak and heterogeneous. Interestingly, gene expression analysis has shown that PMBCL is molecularly distinct from typical DLBCL and shares many components of the molecular signature with classic Hodgkin lymphoma (cHL). It had long been speculated that there may be a pathogenic overlap between the nodular sclerosis subtype of cHL based on shared clinical features, including a young age of onset and mediastinal predominance, as well as pathologic features, including predominant fibrosis and tumor cells that are $CD30^+$. In addition, composite and sequential lymphomas have been reported, and a gray zone lymphoma (GZL) with overlapping features of both malignancies is now defined in the WHO classification (see the section "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL"), further highlighting the biological continuum between these diseases.

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A novel recurrent translocation involving *CIITA* (Major Histocompatibility Complex (MHC) class II transactivator), found to be recurrent in PMBCL and occurring in 38% of patients, is also found in 15% of cHL. Cases with these chromosomal breaks have an inferior disease-specific survival. Prior studies also found reduced expression of MHC class II genes, which also is linked to an inferior outcome. Additionally, PMBCL often has 9p24.1 amplification that results in increased expression of PD-1 ligand, which is a rational therapeutic target (discussed later).

The outcome of patients with PMBCL is generally favorable, with a 5-year PFS of 70% when patients are treated with R-CHOP, though approximately 20% of patients have primary induction failure that can be very difficult to salvage. Given the typical bulky localized presentation, most patients have historically also received consolidative radiation therapy, which exposes this population of predominantly young women to late radiation risks, including breast cancer and heart and lung disease. The significant rate of primary refractory disease with R-CHOP and the need for radiation therapy in the majority of patients prompted evaluation of DA-EPOCH-R without radiation in a phase 2 study at the National Cancer Institute. Fifty-one patients (median age, 30 years) were treated. Fifty-nine percent of patients were female, 65% had bulky disease (≥10 cm), and 29% had stage IV disease. At a median follow-up of 5 years, 93% of patients were event-free, and the OS was 97%. These data have resulted in widespread adoption of DA-EPOCH-R without radiation therapy as the upfront treatment of choice for most patients with PMBCL.

Relapsed PMBCL is treated similarly to other relapsed DLBCLs, with second-line chemoimmunotherapy and HDC/ASCT being the treatment of choice for patients with chemosensitive disease. Unfortunately, PMBCL is often highly chemoresistant at the time of progression and has been historically very difficult to salvage with conventional therapy. For patients relapsing after ASCT, or not eligible for ASCT because of chemorefractory disease, options would include CAR T-cell therapy (axicabtagene ciloleucel or lisocabtagene maraleucel) or pembrolizumab, both of which are FDA-approved for R/R PMBCL.

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL

Introduced in the WHO 2008 classification, this diagnosis was defined by overlapping clinical, morphological, or immunophenotypic features between cHL and DLBCL, particularly PMBCL. These cases of GZL usually occur in young men between 20 and 40 years old who frequently present with bulky mediastinal disease. A less common presentation occurs in older adults and may be associated with extranodal advanced-stage lymphoma. A broad spectrum of cytological appearances can occur within the same tumor. The immunophenotype often is transitional between PMBCL and cHL with the tumor cells expressing $CD45^+$, $CD20^+$, $CD30^+$, and $CD15^+$. Cases of morphologically nodular sclerosis cHL with strong and uniform expression of CD20 and CD15 would favor a diagnosis of GZL. In contrast, cases resembling PMBCL but that are $CD20^-$ and $CD15^+$ or EBV-positive, also would support a diagnosis of GZL. Given the challenge associated with making this diagnosis accurately, opinion from expert hematopathologists should be sought. Clinical outcomes appear inferior in GZL compared to PMBCL or cHL, but higher remission rates have been observed with DLBCL-type regimens, such as R-CHOP or DA-EPOCH-R rather than standard Hodgkin lymphoma therapy. Because of increased risk of chemoresistance in this subset, consolidative radiation therapy should be considered in patients with localized disease.

T-cell/histiocyte-rich DLBCL

T-cell/histiocyte-rich DLBCL is an uncommon variant of DLBCL, which usually presents at advanced stage with frequent involvement of liver, spleen, and bone marrow. Typically, the neoplastic cells comprise <10% of the cellular population and are outnumbered by a background of abundant T cells and histiocytes. Histologically, it can resemble nodular lymphocyte predominant HL or can be transformed from a prior diagnosis of nodular lymphocyte predominant HL. Treatment with R-CHOP produces results like DLBCL NOS and remains the standard of care.

High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit lymphoma)

Five to 10 percent of DLBCL patients have DHL, defined as the presence of *MYC* and *BCL2* or *BCL6* translocations (detected by FISH or karyotype). These cases have mutational features, and frequently morphologic features, intermediate between DLBCL and BL and have been reclassified in the 2017 WHO classification as *high-grade B-cell lymphoma with* MYC *and* BCL2 *and/or* BCL6 *rearrangements*. These high-risk patients have lower OS when treated with R-CHOP; therefore, R-CHOP is considered an inadequate therapy for patients with DHL, who have a median OS of approximately 2 years.

Most patients present with poor prognostic features, including advanced age, elevated LDH, and advanced stage, and often have extranodal involvement, including CNS. Patients may present with circulating leukemic-phase

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disease, which is extremely uncommon in typical cases of DLBCL. Because of the inadequacy of R-CHOP therapy, various intensified chemoimmunotherapy strategies have been used, largely based on experience in BL; however, poor performance status can limit the use of highly intensive chemotherapy. Because of the rarity of DHL, data largely come from retrospective reviews, making comparison between regimens difficult. The intensified upfront induction regimens, including R–hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD)/methotrexate and cytarabine (MA) and R–cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) appear to compare favorably with historical controls treated with R-CHOP; however, one must bear in mind that patients who are candidates for such intensive therapy are frequently younger and have better PS; therefore, results may not be generalizable. In a large retrospective analysis, intensive therapies, including DA-EPOCH-R, perform better than R-CHOP. Additionally, DA-R-EPOCH-R is well-tolerated in older adults compared to more intensive regimens and is listed within the National Comprehensive Cancer Network guidelines as a recommended option. Given the high risk of CNS dissemination, prophylactic therapy for the CNS is recommended. Whether consolidative stem cell transplantation offers additional benefit remains uncertain, but thus far retrospective analyses have not identified a clear benefit for transplantation in first remission for DHL. Novel agents for this disease are under investigation and are clearly needed. Encouragingly, patients with chemotherapy-refractory DHL have been shown to have responses to anti-CD19 CAR T-cell therapy analogous to patients with DLBCL NOS, and thus should be considered for this treatment.

KEY POINTS

- DLBCL is the most common histologic subtype of NHL.
- The IPI and COO phenotypes remain prognostic in the rituximab treatment era for DLBCL.
- Treatment with R-CHOP-21 (ie, repeated every 21 days) for 6 cycles is the standard of care in advanced disease; the role of consolidative radiation in advanced disease is not well-defined.
- In limited-stage disease, abbreviated chemotherapy with 3 to 4 cycles of R-CHOP plus IFRT can be used. R-CHOP alone is an option for patients with nonbulky disease who achieve a CR on their PET-CT.
- Presence of relapsed disease should be documented by biopsy whenever possible.
- Transplantation-eligible patients with relapsed DLBCL are usually treated with salvage chemotherapy (R-DHAP, R-ICE, and R-GDP appear to have similar efficacy) followed by HDC and stem cell transplantation.
- Anti-CD19 CAR T-cell therapy can induce durable remissions in a significant proportion of chemotherapy-refractory DLBCL, PMBCL, and transformed FL.
- PMBCL patients should preferentially be treated with DA-EPOCH-R without RT, though there are no randomized studies in this disease.
- High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (DHL) represents a particularly poor prognostic category when treated with R-CHOP; the disease is usually treated with more intensive regimens.

Primary CNS lymphoma

Primary CNS lymphoma (PCNSL) occurs in the brain parenchyma, spinal cord, eye, cranial nerves, or leptomeninges without systemic involvement. Of note, although 95% of cases of PCNSL are DLBCLs, rare cases of peripheral T-cell lymphoma (PTCL), low-grade lymphoma, and BL also have been reported. In addition to B-cell markers, CD10 expression is observed in only 10% to 20% of cases, but *BCL6* expression is common (60% to 80%). Most cases (>90%) are of the ABC-like subtype of DLBCL. Mutations of *CD79B*, *MYD88*, and *PIM1* are frequently observed. Amplifications of 9p24.1 are common and result in PD-L1 expression in most cases. PCNSLs are rare and may occur in immunocompetent patients or in association with immunosuppression related to HIV infection or to organ and marrow transplantation. With the introduction of combination antiretroviral therapy (cART), the incidence of PCNSL has decreased in HIV-infected persons. It appears, however, to be increasing in incidence in immunocompetent patients. In the latter group, the median age is 60 years, and it is discovered based on focal neurologic symptoms, mental status changes, or symptoms of increased intracranial pressure. Ocular involvement can occur in 10% to 20% of patients and may be the sole site of disease at presentation (intraocular lymphoma). Concurrent leptomeningeal disease is found in 16% of patients through colony-stimulating factor (CSF) analysis, but occurs as the sole site in <5%. B symptoms, systemic symptoms of fever, night sweats, and weight loss, are extremely uncommon and should raise suspicions of systemic involvement.

Stereotactic guided biopsy is the optimal method for diagnosing CNS lymphoma; gross total resection should be avoided. Steroids can interfere with pathologic diagnosis, and if they are started for neurologic symptoms, they

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should be withheld in patients with a presumptive radiologic diagnosis of CNS lymphoma to increase diagnostic biopsy yield. A contrast-enhanced magnetic resonance imaging (MRI) should be performed, along with lumbar puncture with CSF analysis by flow cytometry. A slit-lamp examination should be performed to rule out concurrent ocular involvement. Staging should include full body PET/CT imaging, MRI of the spinal axis, and, in men, testicular ultrasound because 4% to 12% of patients can have extraneural disease.

A prognostic scoring system has been developed for PCNSL, given the limitations of the Ann Arbor staging system and the IPI in this disease. The following 5 factors are associated with a poor prognosis: age older than 60 years, PS > 2, elevated LDH, high CSF fluid protein concentration, and tumor location within the deep regions of the brain. Patients with 0, 1 to 4, or 5 of these factors have 2-year OS rates of 80%, 48%, or 15%, respectively.

The median survival after surgery alone is ~1 to 4 months. Whole-brain radiation is associated with a high response rate of 90%, but the median survival is only 12 months, and patients can develop significant cognitive dysfunction. CHOP has poor CNS penetration and should not be used in PCNSL. The exception is intravascular large B-cell lymphoma with CNS involvement because the mechanism of spread is likely different. Although there have been no randomized controlled studies to establish the best therapy, in retrospective analyses, outcomes are superior when high-dose methotrexate (HD-MTX) (3 to 8 g/m^2) is incorporated into first-line regimens. With this approach, the 5-year OS is 30% to 40%. Some studies have added other CNS-penetrant chemotherapy drugs, such as Ara-C, procarbazine, vincristine, temozolomide, and thiotepa. Rituximab therapy also appears to improve outcome. A phase 3 trial randomizing younger patients in a CR following HD-MTX to Whole Brain Radio Therapy (WBRT) (45 Gy) or observation demonstrated an improvement in median PFS (18 months versus 12 months) but OS was similar, and toxicity was greater in patients who received radiation. For patients older than 60 years, the risks of neurotoxicity are considerable and manifest as dementia, ataxia, and incontinence, with a median time to risk onset of approximately 1 year. Because of concerns of neurotoxicity even in younger patients, numerous studies are evaluating chemotherapy alone with CNS-penetrant drugs.

The Cancer and Leukemia Group B (CALGB) evaluated the combination of HD-MTX, temozolomide, and rituximab (MRT) with consolidative HDC using Ara-C and etoposide without WBRT; the 3-year PFS and OS were 50% and 67%, respectively. The International Extranodal Lymphoma Study Group (IELSG) conducted an important randomized trial, first randomizing patients to 1 of 3 induction arms: methotrexate and cytarabine (MA); methotrexate, cytarabine and rituximab (MAR); and methotrexate, cytarabine, thiotepa and rituximab (MATRix). For responding patients, a second randomization assigned patients to WBRT versus HDC/ASCT. Results from the initial randomization showed that the MATRix combination resulted in the highest PFS and OS, followed by MAR, and then by MA. MATRix is therefore an appropriate standard of care in patients sufficiently fit to undergo this intensive chemotherapy approach. Rituximab, MTX, vincristine, and procarbazine has also been studied as an induction regimen with reasonable ORR (79% to 94%) and 2-year PFS results (57% to 79%) when followed by consolidation. Until recently, there were no prospective studies defining the best consolidation approach (HDC/SCT, maintenance HD-MTX, cytarabine/etoposide consolidation, WBRT, or observation). CALGB 51101 was designed to compare myeloablative (HDC/ASCT) therapy to nonmyeloablative chemotherapy as consolidation in newly diagnosed CNS lymphoma patients. All patients (n = 108) received MRT for 4 cycles followed 1 cycle of cytarabine (MRTA) and then were randomized to receive ASCT or etoposide/cytarabine consolidation. With a median follow-up of 3.8 years the median PFS in the ASCT arm was substantially longer (6 years versus 2.4 years) however it should be noted that more patients on the chemotherapy consolidation arm experienced progression or death before undergoing consolidation.

The second randomization in the IELSG trial is based on increasing evidence of benefit for a thiotepa-based ASCT in CNS lymphomas. Several small phase 2 studies have evaluated upfront transplantation with cure rates ranging from 40% to 77% using a variety of lead-in chemotherapy and HDC regimens. In patients with relapsed or refractory primary CNS, HDC/ASCT is associated with a 2-year OS of 45%, a Transplant Related Mortality (TRM) of 16%, and severe neurotoxicity in 12%. The second randomization of the IELSG trial found identical 75% 2-year PFSs between HDC/ASCT and WBRT but with significant neurotoxicity in the WBRT arm, which therefore favors ASCT consolidation. A Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang (GOELAMS) study comparing HDC/ASCT to WBRT as consolidation showed a 2-year PFS benefit favoring the transplantation arm, and less cognitive impairment than with WBRT. These data do support consideration of HDC/ASCT consolidation rather than WBRT in young patients sufficiently fit to undergo transplantation.

Maintenance therapy (temozolomide, procarbazine, or lenalidomide) has also been studied in elderly patients who are not candidates for intensive consolidation strategies.

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For relapsed patients, methotrexate-based therapy is usually used again, particularly in those who have had a lengthy remission after initial therapy. Temozolomide alone or in combination with rituximab has shown an ORR of 26% and 53%, respectively, in relapsed and refractory patients. The combination of high-dose MRT is well tolerated and associated with significant clinical activity in a small phase 2 study. CR was achieved in 14/18 (78%) patients at a median of 4 months. Three of 18 patients achieved a PR. At a median follow-up of 15.5 months from treatment initiation, 10/18 patients remain in CR and median PFS has not been reached. Novel biologically directed therapies are also emerging in the management of relapsed/refractory PCNSL. The ABC subtype, which characterizes nearly all cases of primary CNS DLBCL, makes lenalidomide, pomalidomide, or ibrutinib appealing agents; both agents have demonstrated high response rates in small phase 1 or 2 studies. The 9p24.1 amplification and PD-L1 expression make PD-1 inhibitors a potential option, and indeed small initial series have shown high and durable rates of remission. All 3 of these novel agents (lenalidomide, ibrutinib, and PD1 inhibitors) warrant ongoing study in combination in the relapsed setting, as well as incorporation into frontline therapy.

Secondary CNS lymphoma

The rate of secondary CNS involvement in aggressive lymphoma and lymphoblastic lymphoma and BL (see section on Burkitt lymphoma in this chapter), varies by histology. In these highly aggressive lymphomas, CNS prophylaxis is routinely incorporated using intrathecal and systemic chemotherapy with or without cranial irradiation and has been shown to reduce the rate of CNS relapse and to prolong survival. Secondary CNS lymphoma may also be seen in DLBCL occurring in the brain parenchyma, leptomeningeal compartment, or both as an isolated event or with systemic relapse. Approximately 1% of patients with DLBCL have CNS involvement at diagnosis; the risk of subsequent CNS recurrence is approximately 4% but is increased in selected high-risk subgroups. Several extranodal sites have been associated with a higher risk of CNS relapse, including testis, kidney, and bone marrow (concordant). To create a robust risk model predictive of CNS recurrence risk, known as the CNS-IPI, the German High-Grade Lymphoma Study Group analyzed data on 2164 patients treated with R-CHOP or R-CHOP–like therapy. The risk of CNS involvement was 3%, and adverse risk factors for CNS relapse on multivariable analysis were the 5 established IPI risk factors, plus renal or adrenal involvement. Using the total of these 6 risk factors present at diagnosis, 3 risk groups were created: low risk (0-1), intermediate risk (2-3), or high risk (4-6), with CNS relapse rates of 0.6%, 3.4%, and 10.2%, respectively. These data were validated in a 1600-subject retrospective cohort from the British Columbia Cancer Agency and yielded similar results. Based on these data, patients with 4 to 6 CNS-IPI risk factors present at diagnosis would be classified as high risk for CNS recurrence and should be considered for CNS prophylaxis strategies.

Although these and other studies can effectively identify subgroups with a high risk for CNS disease, demonstrating a benefit for CNS prophylaxis has proven to be much more difficult in DLBCL. Furthermore, many of the studies evaluating CNS prophylaxis were published before the routine use of rituximab, which does appear to reduce risk, albeit to a modest degree. The RiCOVER-60 study evaluated 1217 patients with aggressive lymphoma (81% DLBCL) and reported that 58 patients (4.8%) developed CNS relapse or progression with a median time of 8 months (1-39 months); the median survival from CNS relapse was only 3 months. Those patients who received rituximab had a lower risk of CNS relapse; however, the magnitude of difference was very small (3.6% versus 5.9%, $P = 0.043$). Other studies have confirmed that rituximab appears to reduce the risk of relapse, particularly in patients in a CR, suggesting the benefit, in part, may result from better systemic disease control. The risk is not altogether eliminated, however, given the poor CNS penetration of rituximab. Prophylactic intrathecal chemotherapy is incorporated into more intensive chemotherapy regimens but is not recommended as the preferred route for CNS prophylaxis in DLBCL NOS. Prophylactic use of HD-MTX (3.0 to 3.5 g/m^2) with R-CHOP was evaluated retrospectively in 65 patients with high-risk DLBCL (elevated LDH, involvement of >1 extranodal sites, 4 to 5 Hollender criteria, high-risk location [bone marrow, testes, epidural, liver, adrenal, renal, orbit]), and reported a low rate of CNS relapse (3%). Use of HD-MTX, however, is limited in elderly patients, particularly in those with poor renal function.

Despite the limitations and lack of evidence-based data to direct treatment, patients considered high-risk by the extranodal site involved or by the CNS-IPI model should be considered for CNS prophylaxis. Patients with any neurologic signs or symptoms should also be evaluated with diagnostic lumbar puncture including flow cytometry and brain MRI as appropriate. Our preferred method for CNS prophylaxis in eligible patients is systemic methotrexate 3.5 g/m^2 administered on day 15 of the 21-day R-CHOP-M cycle and usually administered with alternating cycles for a total of 3 methotrexate infusions, if

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tolerated. Intrathecal prophylaxis remains available for patients who are not considered candidates for systemic methotrexate therapy.

Burkitt lymphoma

BL is among the most aggressive of all human malignancies, with a rapid doubling time, acute onset, and progression of symptoms. Histologically, BL has a diffuse growth pattern of medium-size cells and a high mitotic rate; nearly 100% of cells are Ki-67 positive because of deregulated high-level expression of *cMYC* arising from reciprocal translocation with immunoglobulin heavy- (t8;14) or variant light-chain gene loci [t(2;8) or t(8;22)] (Table 23-4). Additional mutations in the transcription factor that controls germinal center cell proliferation, *TCF3*, and its inhibitor, *ID3*, also cooperate with *cMYC* overexpression to drive proliferation. There is also a high rate of cell death or apoptosis, and the dead cells are phagocytosed by histiocytes, which gives a "starry-sky" appearance. The B cells are positive for CD19, CD20, *BCL6*, and CD10. *BCL2* is usually negative, but rare weakly positive cases may be seen. Lack of terminal deoxynucleotidyl transferase is critical to rule out ALL/lymphoblastic lymphoma. Recent studies have identified a subset of lymphomas that resemble BL by clinical course, morphology, immunophenotype, and gene expression, but lack *MYC* rearrangements. This new provisional 2016 WHO entity has chromosome 11q alterations that appear to drive the Burkitt-like features (Table 23-1).

Originally described in its endemic form in African children presenting with jaw or facial masses, BL also occurs in sporadic form in the Western world, predominantly in children and young adults. It also is seen in HIV-infected patients. Nearly all endemic cases show evidence of Epstein-Barr virus (EBV) infection, but such EBV infection is present in only a minority of sporadic cases.

Clinically, patients with BL frequently present with a bulky abdominal mass, B symptoms, high LDH, and extranodal disease, including bone marrow involvement, is common (up to 70%). A leukemic phase can be seen, but pure acute leukemia is extremely rare. CNS dissemination, usually in the form of leptomeningeal involvement, may be present at diagnosis in up to 30% of patients. As a result, CNS chemoprophylaxis is integrated into the therapy for virtually all BL patients. CNS involvement is associated with a lower rate of complete remission and inferior overall survival. CNS irradiation is typically omitted and is reserved for adult patients with overt CNS disease.

The BL IPI was developed as a prognostication tool and for use stratifying BL patients on clinical trials. Taking age, PS, degree of LDH elevation and presence of CNS involvement into account, low-intermediate and high-risk groups were identified with substantially different PFS and OS. In the largest real-world analysis of Burkitt lymphoma outcomes published to date from 30 US centers, age ≥40 years, LDH ≥3× upper limit of normal, ECOG PS ≥2, and CNS involvement were associated with inferior OS.

Therapy for BL must be instituted quickly because of the rapid clinical progression of the disease. Hospital admission and tumor lysis precautions are essential and include vigorous hydration and allopurinol with close monitoring of laboratory studies, including electrolytes and renal function. Recombinant uric acid oxidase (rasburicase) has been shown to be very effective in preventing uric acid nephropathy and can be used to manage hyperuricemia. Serious toxicity, including infectious complications, nephrotoxicity, or hepatotoxicity, is frequent, but treatment mortality is low. To reduce the large tumor bulk often present at diagnosis and to limit the severity of tumor lysis syndrome, a prephase, consisting of a week of glucocorticoid treatment and a dose of vincristine and cyclophosphamide before intensive chemotherapy, has often been incorporated into treatment regimens.

Multiple studies have shown that CHOP chemotherapy is inadequate for the treatment of BL, and intensified therapies result in higher cure rates. Multiagent combination chemotherapy, that includes high doses of alkylating agents and CNS prophylaxis, have improved the outcome for adults and children with the disease.

Because the lymphoblasts in mature B-cell NHL exhibit strong expression of CD20, several studies have incorporated the anti-CD20 monoclonal antibody rituximab into frontline regimens to further improve outcome. Evidence that addition of rituximab to a short intensive chemotherapy program improves EFS in adults with Burkitt leukemia or lymphoma was also demonstrated by a randomized phase 3 trial of 260 adult patients with untreated HIV-negative BL who received chemotherapy (lymphome malin de Burkitt) with or without rituximab (375 mg/m^2) on day 1 and day 6 during the first 2 courses of chemotherapy (a total of 4 infusions). Three-year EFS was significantly better in the rituximab group (75% versus 62%). The addition of rituximab to frontline therapies for Burkitt lymphoma/leukemia has also been tested, with promising results, in children in a German pilot study as well as in a smaller nonrandomized cohort from the Children's Oncology Group. A large American-European-Australian consortium incorporated rituximab into the treatment of high-grade, high-risk, mature B-cell NHL such as Burkitt lymphoma/leukemia using the

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Table 23-4 Phenotypic markers and common chromosomal translocations in selected non-Hodgkin lymphoma subtypes

NHL	sIg	CD5	CD10	CD20	Other	Cyclin D1	Cytogenetics	Oncogene	Function
CLL/SLL	Weak	+	–	Dim	$CD23^+$, $CD200^+$, FMC^-	–	No diagnostic abnormalities★	–	–
Follicular	++	–	+	+	*BCL2*$^+$, *BCL6*$^+$	–	t(14;18)	*BCL2*	Antiapoptosis
Mantle cell	++	+	–	+	Cyclin $D1^+$, $CD23^-$, $CD200^-$, FMC^+	+	t(11;14)	Cyclin D1	Cell cycle regulator
Marginal zone/ extranodal marginal zone lymphoma	+	–	–	+	–	–	t(11;18)	*AP12*-MALT	Resistance to *Helicobacter pylori* treatment
Lymphoplasmacytic lymphoma	++	–	–	+	$CD25^{+/-}$, $CD38^{+/-}$	–	–	*MYD88*	Proliferation
Hairy cell leukemia	++	–	–	+	$CD11c^+$, $CD25^+$, $CD103^+$, $BRAF^+$	Weak	–	*BRAF*	Proliferation
DLBCL	+	Rare	+/–	+	Variable	–	t(14;18), t(3;14), t(3;v)	*BCL2*	Antiapoptosis
							t(8;X)	*BCL6*	Transcription factor
								cMYC	Proliferation
								EZH2‡	Histone modifier
								MYD88§	Proliferation
PMBCL	–	–	–/+	+	$CD30^{+/-}$, $CD23^{+/-}$, $PD\text{-}L1^{+/-}$	–	t(16;X)†	*CIITA*	MHC class II trans-activator
Burkitt lymphoma	+	–	+	+	*BCL6*$^+$, *MYC*$^+$, TdT^-, *BCL2*$^-$	–	t(8;14), t(2;8), t(8;22)	*cMYC*	Transcription factor
								TCF3/ID3	Transcription factor and its negative inhibitor
ALCL, ALK positive	–	–	–	–	$CD30^+$, $CD2^{+/-}$, $CD3^{-/+}$, ALK^+, EMA^+	–	t(2;5)	*ALK*	Tyrosine kinase
ALCL, ALK negative	–	–	–	–	$CD30^+$, $CD2^{+/-}$, $CD3^{-/+}$, ALK^-, EMA^-	–	t(6;7) (p25.3;q32.3)	*DUSP22*	Phosphatase

MALT, mucosa-associated lymphoid tissue; sIg, surface immunoglobulin; TdT, terminal deoxynucleotidyl transferase.

★A number of prognostic cytogenetic abnormalities have been identified (see Chapter 22).

†A number of partner chromosomes described.

‡Exclusively in GCB-like DLBCL.

§Exclusively in ABC-like DLBCL.

lymphome malin de Burkitt backbone that showed markedly prolonged EFS and OS with rituximab, though at the expense of hypogammaglobulinemia and higher infection risk.

Magrath et al at the National Cancer Institute demonstrated a risk-adapted strategy that is useful for treatment stratification in both adults and children. Low-risk patients were those with a single extra-abdominal mass or completely resected abdominal disease and a normal LDH, and all other patients were considered high-risk. Low-risk patients received 3 cycles of CODOX-M, and high-risk patients received CODOX-M alternating with IVAC for a total of 4 cycles (ie, 2 cycles each of CODOX-M and IVAC). All patients received intrathecal chemoprophylaxis with each cycle, and those with CNS disease at presentation received additional intrathecal therapy during the first 2 cycles. Approximately half of the patients were adults, and the 2-year EFS for all patients was 92%. Two other phase 2 studies have used the Magrath regimen with modifications. In a United Kingdom study, adult (age range, 16 to 60 years; median age, 26.5 years), non-HIV patients were treated with dose-modified CODOX-M

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($3\ g/m^2$) for 3 cycles if they were determined to be low risk (ie, normal LDH, PS of 0 or 1, Ann Arbor stage I or II, and no tumor mass >10 cm), and all other patients were considered high risk and treated with alternating dose-modified CODOX-M/IVAC. The 2-year PFS for the patients with BL was 64%. A modified Magrath regimen was also studied in an older population of patients (median age, 47 years) with a reported 2-year EFS of 71%.

Other therapeutic approaches have included the HyperCVAD/methotrexate-cytarabine regimen. Retrospective analyses and a phase 3 trial evaluating the addition of rituximab to intensive chemotherapy for BL in adults demonstrated an improvement in PFS and established that rituximab should routinely be included in the treatment plans for these patients.

Notably, these intensive regimens incur high rates of toxicity and are poorly tolerated by older adults. The results from 12 large treatment series (10 prospective and 2 retrospective) were combined to better determine outcome in patients with BL in patients older than 40 years. In total, 470 patients were identified, 183 of whom were older than 40 years. The median OS at 2 years with intensive short-duration chemotherapy in older patients was only 39% compared with 71% when all patients were considered, suggesting an unmet need in older BL patients.

A phase 2 study at the National Cancer Institute evaluated DA-EPOCH-R in 30 adult patients with BL. The treatment was well-tolerated in older adults and produced a 5-year EFS of more than 90%. This approach was then validated in a multicenter prospective phase 2 trial of 113 adults with BL treated at 22 centers in the United States. At a median follow-up of 3 years, the EFS was 85.7%; treatment was equally effective in younger and older patients. Based on these data, DA-EPOCH-R can be considered an appropriate standard regimen for the treatment of BL and is preferred in older adults

This regimen (DA-EPOCH-R) has also been used in a multicenter risk-adapted study in adult Burkitt lymphoma. Patients were classified as low risk (stage I or II, normal LDH, mass ≤7 cm, and PS of 0 or 1) or high risk. Low-risk patients received 3 cycles of dose-adjusted EPOCH-R without CNS prophylaxis while high-risk patients received 6 cycles with CNS prophylaxis. With a median follow-up of 58 months, the EFS in low-risk patients was 100%, making this less-intensive regimen an attractive and potentially less-toxic option for low-risk BL.

If relapse does occur in BL, patients are essentially not salvageable and median overall survival is 3 to 4 months. Efforts to improve therapy by identifying new targetable signaling pathways by comparative genomic analysis have demonstrated a significant association with toll-like receptor signaling, Janus kinase–signal transducer and activator of transcription signaling ($P < 0.01$), and mitogen-activated protein kinase signaling ($P < 0.01$). Within each of these pathways, several kinases were overexpressed, including TLR7, IRAK1, IL-10 receptor, IL-21 receptor PIM1, TYK2, and MAP2K1. Before these treatments can be implemented in the clinic, compounds targeting these pathways will have to be tested as additions to frontline therapy because they are unlikely to be sufficiently effective in the setting of relapsed or refractory disease.

High-grade B-cell lymphoma, NOS

High-grade B-cell lymphoma, NOS, is a new diagnostic entity in the 2016 WHO classification. Previously, B-cell lymphomas with morphologic and genetic features between DLBCL and BL, as well as a large proportion of DHLs (described previously), were classified as *B-cell lymphoma, unclassifiable, with features between DLBCL and BL*. With the new classification scheme, DHLs are now classified as *high-grade B-cell lymphoma with* MYC *and* BCL2 *and/or* BCL6 *rearrangements*. B-cell lymphomas with morphologic and genetic features between DLBCL and BL that lack the gene rearrangements are now classified as *high-grade B-cell lymphoma, NOS*. Because this is a newly classified entity, the prognosis and optimal management of these patients remain undefined. With the removal of the DHL patients from this category, the prognosis for the newly classified patients has likely improved. In the absence of data to guide therapy, most lymphoma specialists prefer more intensive strategies in these patients based on their high-risk histology, such as DA-EPOCH-R, which has been validated as effective in other high-grade B-cell lymphomas.

Immunodeficiency-associated lymphoproliferative disorders

Lymphoproliferative disorders associated with congenital or acquired immunodeficiency state are categorized into 4 different categories in WHO classification (2017): (1) primary immunodeficiency disorders (PIDs), including Wiskott-Aldrich syndrome, ataxia-telangiectasia, common variable or severe combined immunodeficiency, X-linked lymphoproliferative disorder, Nijmegen breakage syndrome, hyper-immunoglobulin (Ig) M syndrome, and autoimmune lymphoproliferative syndrome; (2) HIV infection; (3) post–solid-organ or marrow transplantation with iatrogenic immunosuppression; and (4) methotrexate- or other iatrogenic-related immunosuppression for

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autoimmune disease. The lymphomas seen in these settings are heterogeneous and may include HL or, more commonly, aggressive NHL.

Lymphoproliferative disorders associated with PIDs are most commonly seen in pediatric patients and frequently are associated with EBV infection. In many cases, underlying immune-deficiency syndrome is undiagnosed at the time of presentation. Lymphomas occurring in patients with PID do not differ morphologically compared with immunocompetent hosts. DLBCL is the most frequent histologic type, although T-cell lymphomas are more common in ataxia-telangiectasia. EBV-related lymphomatoid granulomatosis is associated with Wiskott-Aldrich syndrome. These malignancies respond poorly to standard therapy. Therapy depends on both the underlying disorder and the specific lymphoma subtype; allogeneic transplantation has been used successfully in some patients. Novel immunotherapeutic or pharmacologic strategies targeting EBV are being explored.

EBV-positive mucocutaneous ulcer, a newly recognized type of large B-cell lymphoma, occurs in setting of age-related or iatrogenic immunosuppression (Table 23-1). The typical presentation is cutaneous or mucosal ulcers with aggressive histologic features of large transformed EBV-positive B cells. Contradictory to its histologically aggressive features, it has indolent clinical course. Nearly all reported cases responded to reduction of immunosuppressive therapy.

HIV-associated lymphomas

Even after development of cART in late 1990s, the incidence of lymphomas in HIV-infected individuals did not decrease and remains the most common AIDS-related cancer in the developed world. The AIDS-related lymphomas are mostly B cell in origin with advanced disease at presentation and an aggressive clinical course. More often they are associated with EBV and human herpesvirus 8 (HHV-8). Outcomes for the HIV-associated lymphomas were historically poor; however, since the advent of cART, outcomes in the modern era are similar to non-HIV lymphoma as long as the HIV is under good control and the CD4 count is over 200 cells/μL. This highlights the importance of interdisciplinary team approach for the HIV lymphoma management in collaboration with an infectious disease specialist for the best outcome for these patients. The ART and chemotherapy (CTH) have overlapping toxicities, therefore close monitoring throughout the duration of CTH is critically important. Continuation of ART during CTH is preferred approach.

Optimal CTH and the role of rituximab with anthracycline combinations in HIV-associated DLBCL have been the subject of debate. In a randomized phase 3 trial conducted by the AIDS Malignancy Consortium (AMC 010), addition of rituximab to CHOP did not improve the outcome but increased treatment-related infectious deaths. A subsequent analysis, however, indicated that the toxicity was higher in patients with a CD4 count <50. Furthermore, a phase 2 French study using R-CHOP in the HIV-positive aggressive lymphomas (85% DLBCL) demonstrated a 2-year OS of 75% without an increase in life-threatening infections, which also may reflect the exclusion of poor-prognosis patients because patients could have no more than one of the following: CD4 < 100, PS > 2, or prior AIDS. Thus, rituximab should be given to HIV patients if the CD4 count is >50, particularly given the strong evidence for improved survival in the HIV-negative setting. Concurrent administration of granulocyte CSF (G-CSF) is advised, given the high rate of infection in this population, and all patients should receive prophylaxis against *Pneumocystis jirovecii* infection. DA-EPOCH has been tested in the HIV-aggressive lymphoma, the majority of which had DLBCL but with suspension of the cART to avoid drug interactions. At 53 months, the PFS and OS were 60% and 73%, respectively. The AMC also tested EPOCH-R (AMC 034) in patients with the HIV-positive, aggressive B-cell lymphomas with rituximab given concurrently or sequentially; the 2-year OS rates were 63% and 66%, respectively. Use of the cART was at the discretion of the treating physician but was used in the majority of patients. There was no greater risk of infection except in patients with a CD4 < 50. The National Cancer Institute piloted a second-generation regimen short-course (SC)-EPOCH-RR (2 doses of rituximab per cycle), with G-CSF support, in HIV-positive DLBCL patients with the goal of improving efficacy and reducing toxicity. Dose-dense rituximab was intended to enhance the CTH and minimize the number of treatment cycles. A PET scan was performed after 2 cycles: if negative, only 1 more cycle was given; if positive, 2 to 3 cycles were given. The 5-year PFS and OS were 84% and 64%, respectively. A pooled analysis of these 2 AMC trials with patients treated with R-CHOP or R-EPOCH suggested that patients receiving R-EPOCH had an improved EFS and OS after adjusting for the aaIPI and CD4 count. The TRM was greater in patients with CD4 counts <50 (37% versus 6%, $P = 0.01$) regardless of the regimen used. Despite the practice for many years at the NCI to suspend cART use during DA-EPOCH, modern cART regimens can safely be combined with chemoimmunotherapy. The combination is recommended by infectious disease specialists and should be considered the standard of care. Attention should be paid to certain classes of drugs

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that can cause drug-drug interactions, such as the protease inhibitors, which may increase vincristine-associated toxicity. Among the BL patients, both R-CODOX-M/R-IVAC and DA-EPOCH-R can be safely administered to the HIV-BL patients. These patients should therefore be treated similarly to their HIV-negative counterparts. For HIV-related aggressive lymphomas, CNS prophylaxis with intrathecal methotrexate or cytarabine is highly recommended because of the high risk of CNS involvement. For rare HIV-related lymphomas like plasmablastic and primary effusion lymphomas, CHOP/EPOCH-based regimens are reasonable in the absence of prospective trials.

For relapsed HIV-related lymphomas, the treatment is similar to the HIV-negative counterpart. The data remain scarce in this setting. Evidence for novel agents and CAR T in HIV-related lymphoma is very scant and should be used with caution.

Posttransplant lymphoproliferative disorders

The posttransplant lymphoproliferative disorders (PTLDs) occur as a consequence of immunosuppression in recipients of solid-organ, bone marrow, or stem cell allografts. The risk is higher in the solid-organ transplants that warrant a higher degree of immunosuppression (10% to 25% in heart and lung transplants) than those that require a lower degree of immune-suppression (1% to 5% kidney and liver transplants), but the most important risk factor for the PTLD is pretransplant EBV mismatch. It is important to rule out other etiologies such as infection, graft rejection, and graft-versus-host disease (GVHD). Adequate biopsy is the key to diagnose PTLD. The PTLD is divided into 4 groups by WHO classification: (1) nondestructive PTLDs, which include plasmacytic hyperplasia, infectious mononucleosis, and florid follicular hyperplasia; (2) polymorphic PTLD; (3) monomorphic PTLD, which includes B- and T-cell lymphomas and plasma cell neoplasms; (4) cHL PTLD. Importantly, except for the EBV-positive marginal zone lymphoma, indolent small B-cell lymphomas are not considered PTLDs. EBV-negative PTLD has increased over the last decade and typically has a late onset (median time from transplantation to PTLD of 50 to 60 months versus 12 months in EBV-positive patients), a poorer response to therapy, and is more frequently monomorphic.

PTLDs have diverse clinical presentation depending on location. Extranodal involvement is common, particularly the gastrointestinal (GI) tract (~25%), lung, skin, and bone marrow. Primary CNS lymphoma is predominantly seen post–kidney transplant. The goal of treatment is not only to cure the lymphoma but also to preserve graft function. Although a significant minority (20% to 50%) of patients respond to a reduction in intensity of immunosuppressive drugs, most require additional systemic therapy, particularly for monomorphic or late PTLDs. Tolerance to CTH is poor in the PTLD patients, with treatment-related mortality reported to be as high as 31% in older series using CHOP CTH. With historically poor tolerance to combination CTH, single-agent rituximab has been explored in the first-line setting in PTLD. The ORR has ranged from 40% to 75%, and it is extremely well tolerated; however, remission duration may be short in many patients. In the first prospective phase 2 study, 43 PTLD patients who had failed to respond to a reduction in immunosuppression were treated with single-agent rituximab. The ORR was 44% at day 80 (CR 21%), and the 1-year OS was 67%. An updated analysis from this study evaluating 60 patients demonstrated an ORR of 59% (CR 42%), but the median PFS was only 6 months and the 2-year OS was 52%. Elevated LDH was predictive of disease progression as well as a shorter time from the date of transplant. Using a PTLD-adapted prognostic score incorporating age (>60 years), elevated LDH, and PS (>2), patients with a score of 0, 1, or 2/3 had 2-year OS estimates of 88%, 50%, and 0%, respectively, suggesting that single-agent rituximab may be suboptimal in high-risk groups. A subsequent phase 2 study, 152 treatment-naïve patients with PTLD were administered 4 weekly doses of rituximab, with subsequent therapy stratified based on CT scan response. Patients with a CR after rituximab alone received 4 additional doses of rituximab monotherapy at 21-day intervals, while patients without CR proceeded to 4 cycles of R-CHOP-21. Seventy percent of subjects achieved CR after rituximab monotherapy, with the remainder requiring R-CHOP. The 3-year PFS and OS in the entire population were 75% and 70%, respectively, suggesting that this sequential response-adapted treatment approach is a reasonable strategy and may avoid CTH exposure in a significant proportion of patients. Reduced immunosuppression and single-agent rituximab are therefore reasonable first-line treatments in most patients with sequential therapy with R-CHOP reserved for those who do not achieve a CR after reduced immunosuppression and rituximab alone. For patients who present with very high-risk aggressive disease, R-CHOP can be considered frontline treatment with G-CSF support and inclusion of Pneumocystis jiroveci pneumonia prophylaxis.

Mantle cell lymphoma

MCL accounts for 5% to 8% of all NHLs and was considered incurable, with historically poor outcomes and a short overall survival. Modern outcomes have markedly improved for younger and older patients alike, based on

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improved induction regimens, availability of targeted therapies and CAR T-cell therapy at relapse.

MCL has distinctive clinical features including median age in the mid-60s, a striking male predominance, and a strong tendency to present with advanced-stage disease. Extranodal involvement is common, including bone marrow and peripheral blood, plus a peculiar tendency to invade the GI tract, which may present as a distinctive syndrome of lymphomatous polyposis of the large bowel. Even patients without overt colonic polyposis frequently have subclinical GI epithelial invasion, which can be demonstrated on biopsy.

Cytologically, most MCLs consist of small lymphocytes with notched nuclei. The architectural pattern of the lymph node usually is diffuse but may show a vaguely nodular- or mantle-zone growth pattern. A spectrum of morphologic variants has been recognized that includes small cells, which are composed of small round lymphocytes and clumped chromatin, mimicking small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL), and a blastoid variant, which has a high mitotic rate and is clinically very aggressive. The immunophenotype of MCL is distinctive. Cases are typically $CD5^+$, $FMC7^+$, and $CD43^+$, but $CD10^-$ and $CD23^-$ (Table 23-4). Some of the salient features that distinguish MCL from SLL or CLL are the expression of cyclin D1, *SOX11*, and FMC7 without CD23 expression (Table 23-4). Furthermore, MCL has a more intense IgM or IgD and CD20 expression than SLL/CLL. Virtually all MCLs carry the t(11;14)(q13;q32) on karyotypic analysis or by FISH. This reciprocal translocation juxtaposes the immunoglobulin heavy-chain locus and the cyclin D1 (*BCL-1*) gene, resulting in overexpression of cyclin D1.

Biologic and clinical features have prognostic value in MCL. The cellular proliferation index may be the most powerful predictor. A complementary DNA microarray analysis has demonstrated that genes associated with cellular proliferation show striking variability among MCL cases, ranging from low to very high expression. Patients in the lowest quartile of expression have median survival times of 6 to 8 years, whereas patients in the highest expression quartile have survivals of <1 year. For clinical practice, Ki-67 staining can provide an estimate of proliferation. Three prognostic groups have been identified using cut points of <10% (best), 10% to 29% (intermediate), and >30% (worst). With regards to clinical factors, the IPI does not provide adequate prognostic usefulness when applied to MCL, leading to the generation of an MCL-specific index. The MCL international prognostic index (MIPI) identified 4 clinical features, age, PS, LDH, and white blood cells, as independently associated with OS (Table 23-5). The MIPI score can separate patients into 3 risk groups and is quite valuable for characterizing patients in a clinical trial. This characterization is not useful in clinical practice for therapeutic decision making.

Two types of clinically indolent MCL variants have been recognized. One is in situ mantle cell neoplasia (Table 23-1), with the term *neoplasia* replacing *lymphoma* to emphasize the low rate of progression of this variant, which is characterized by the presence of cyclin D1-positive cells in the mantle zones of otherwise normal follicles without evidence of nodal architectural disruption. Likewise, the second indolent MCL variant is a leukemic nonnodal MCL that is likely derived from a post–germinal center B cell (*IGHV* mutated) that usually lacks *SOX11* expression. Patients with this variant typically present with peripheral blood lymphocytosis and splenomegaly without significant lymphadenopathy.

TP53-mutated MCL is a distinctively aggressive subtype associated with blastoid morphology, high proliferative index, high-risk MIPI score, and resistance to intensive induction therapy. The *TP53* mutation is independently associated with inferior outcome, with a median overall survival of 1.8 years.

Management of newly diagnosed MCL

Initial therapy for MCL must be personalized to the patient, considering pathology, clinical presentation, age, and comorbidities. Being resistant to aggressive CTH, *TP53*-mutated MCL might need a different approach. At this time, consensus guidelines are lacking for this highly aggressive variety of MCL.

Patients with low disease burden and asymptomatic MCL may safely be observed for a period of time, though most patients require therapy. The indolent variants of MCL, which most commonly present with leukemic disease and splenomegaly with minimal adenopathy, are

Table 23-5 The Mantle Cell Lymphoma International Prognostic Index

Points	Age, y	ECOG PS	LDH/ULN	WBC, cells/mm^3
0	<50	0-1	≤0.67	<6700
1	50-59	—	0.67-0.99	6700-9999
2	60-69	2-4	1.00-1.49	10,000-14,999
3	≥70	—	≥1.50	≥15,000

MIPI risk factors are age, PS, LDH, WBC level.

Formula for MIPI: [0.03535 × age (years)] + 0.6978 (if ECOG >1) + [1.367 × $\log_{10}$(LDH/ULN)] + [$\log_{10}$(WBC count)].

Simplified MIPI: low risk, 0-3 points; intermediate risk, 4-5 points; high risk, 6-11 points.

ULN, upper limit of normal; WBC, white blood cell.

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particularly good candidates for a period of observation if asymptomatic. Patients in need of therapy are typically divided based on age (usually 65 or younger) and whether they are candidates for HDC/ASCT.

For younger patients with MCL, the strategies incorporating rituximab, cytarabine, and HDC/ASCT consolidation have produced the best results with the longest PFS and OS. The Nordic Lymphoma Study Group phase 2 trial tested an intensive induction immunochemotherapy (in ≤65 years, median 56 years) with cycles of R-maxi-CHOP alternating with R-cytarabine followed by consolidative ASCT for responding patients. The ORR was 96%, and at 15 years of follow-up, the median PFS and OS were 8.5 years and 12.7 years, respectively. In a phase 3 randomized trial in MCL patients younger than 65 years by the European MCL Network, the efficacy of 6 courses of R-CHOP followed by HDC/ASCT versus alternating courses of R-CHOP/R-DHAP followed by a high-dose cytarabine containing HDC/ASCT was compared. The study was designed to test the contribution of cytarabine in the management of younger MCL patients (median age 56 years). The 5-year PFS was significantly better in the cytarabine-containing arm (65% versus 40%). A recent prospective phase 3 trial from the French LYSA group administered 4 cycles of R-DHAP followed by HDC/ASCT in responding patients, who were then randomized to maintenance rituximab therapy versus no further therapy. The ORR and Complete Response Rate (CRR) after 4 courses of R-DHAP were 89% and 77%, respectively. Among randomized patients, the 4-year PFSs were 83% versus 64%, respectively, favoring maintenance rituximab. The 4-year OSs were also improved (89% versus 80%, respectively, $P = 0.04$), making maintenance rituximab the standard of care post HDC/ASCT in MCL. The role of minimal residual disease in deciding the benefit of the HDC/ASCT is being investigated in EA4151 clinical trial.

The patients over the age of 60 have been evaluated in clinical trials without HDC/ASCT. The European MCL Network conducted a trial for patients older than 60 years (median age, 70 years), who were assigned randomly to induction with R-CHOP or R-FC (rituximab, fludarabine, cyclophosphamide) regimen. Responding patients underwent a second randomization to maintenance therapy with rituximab (MR) or interferon-α (IFNα), until progression. Although the response rates were similar between R-CHOP (86%) and R-FC (79%), the OS was significantly better in the R-CHOP arm (62% versus 47% at 4 years, $P = 0.005$). The inferior survival in the R-FC group was caused by a combination of inferior disease control and increased death from infectious complications related to the immunosuppressive effects of fludarabine. The remission duration was significantly longer in the rituximab group than in the IFN group. At 4 years, 58% of the MR group remained in remission compared with 29% of the IFN group. The subgroup analysis indicated the benefit of the MR was restricted to the R-CHOP-treated patients; the R-CHOP plus MR-treated patients experienced improved 4-year OS compared with R-CHOP- plus IFN–treated patients (87 versus 63%, $P = 0.005$), respectively. This trial indicates that the R-CHOP followed by MR is a reasonable frontline approach for the older MCL patients.

An additional phase 3 trial compared R-CHOP to an R-CHOP-like regimen (VR-CAP), where bortezomib replaced vincristine. The VR-CAP regimen was superior to R-CHOP for complete response rates (53% versus 42%), median PFS (24.7 months versus 14.4 months), and 4-year OS rate (64% versus 54%). The rates of neutropenia and thrombocytopenia were higher in the VR-CAP patients. Finally, BR also appears to be a preferred alternative to R-CHOP. Combination of BR and R-cytarabine has shown impressive activity in MCL. In a phase 2 study, BR with cytarabine (R-BAC) was evaluated in newly diagnosed MCL patients. The doses of bendamustine (70 mg/m^2) and cytarabine (500 mg/m^2) were reduced to improve hematological toxicities. R-BAC was overall well tolerated with impressive 91% CRR. BR and R-cytarabine, sequential and alternate administration approaches are being further evaluated. A large, randomized trial compared BR with R-CHOP in the patients with newly diagnosed indolent and MCL lymphoma. For the entire study population, BR was better tolerated than R-CHOP, with less alopecia, neutropenia, and infections. In the MCL patients ($n = 93$), median age 70, BR was superior to R-CHOP for median PFS (35 months versus 22 months, $P = 0.006$). In a similarly designed trial conducted in North America, MCL patients ($n = 67$) were a subset of the study population. MCL patients assigned to BR were more likely to achieve complete remission than patients assigned to R-CHOP or R-CVP (50% versus 27%). Taken together, these studies suggest that the VR-CAP and BR regimens are reasonable alternative to R-CHOP regimens in elderly patients with MCL, with BR being the best tolerated and most widely used. A small, randomized trial evaluating MR after BR in MCL showed no improvement in this setting; therefore, BR without MR remains preferred when BR induction therapy is used.

Management of relapsed MCL

MCL is still considered an incurable lymphoma with a relapsing and remitting clinical course. With each relapse, the PFS gets shorter. Importantly, a duration of first remission of less than 24 months is associated with inferior outcome. BTKi is an important addition for relapsed

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MCL. Ibrutinib, acalabrutinib, and zanubrutinib are approved for relapsed MCL. Ibrutinib, in a phase 2 pivotal study (PCYC-1104-CA, $N = 111$) in relapsed MCL, showed ORR of 68% and CRR of 21% with median PFS of 13.9 months. Acalabrutinib, in a phase 2 pivotal study (ACE-LY-004, $N = 124$) in relapsed MCL, showed ORR of 80% with CRR of 20% with median PFS of 20 months. Zanubrutinib, in a phase 1 BGB-111-AU-003 study ($n = 37$), showed ORR of 87% and CRR 30% based on CT response criteria. BTKi is mostly considered standard second-line therapy for MCL. R-BAC has shown impressive ORR of 83% in relapsed MCL, especially post BTKi, with median PFS of 10 months. For older patients, the BR regimen is highly active in relapsed MCL, with an ORR of 75% to 92% reported in 2 small studies. Lenalidomide is also active in MCL. In the EMERGE study ($N = 134$), lenalidomide produced ORR of 28% with median duration of response of 16.6 months. In combination with rituximab, lenalidomide produced ORR of 57% ($N = 52$) with median PFS of 11 months. Bortezomib, a proteasome inhibitor, is also approved for relapsed MCL with ORR of 33% and median PFS of 6 months. The mTOR inhibitor temsirolimus is approved in the European Union for relapsed MCL, demonstrating on ORR of 22% and median PFS of 4.8 months in a pivotal study. Venetoclax, a *BCL2* inhibitor, has shown impressive activity as a single agent and in combination with ibrutinib in relapsed MCL.

Younger fit patients relapsing after the intensive therapies are candidates for allo-SCT. A multicenter experience using a reduced-intensity conditioning (RIC) approach demonstrated 2-year EFS and OS rates of 50% and 53%, respectively. The 2-year transplant-related mortality rate was 32%, highlighting the high-risk/high-reward nature of allo SCT in relapsed MCL. The chimeric antigen receptor-T cell (CAR T) therapy has emerged as a very promising cellular therapy for relapsed MCL. Brexucabtagene autoleucel (KTE-19), now FDA-approved, is an autologous CAR T targeting CD19. It was approved based on a pivotal phase 2 study (ZUMA-2). ZUMA-2 had 74 patients leukapheresed and 68 patients received the CAR T product. The ORR for all 74 patients was 85%, with the CRR being 59%. Amongst 60 treated patients, 12-month PFS was 61%. Importantly, brexucabtagene autoleucel was effective in the *TP53*-mutated, blastoid, and high MIPI relapsed MCL.

Peripheral T-cell lymphomas

PTCLs represent 10% to 15% of all NHLs in Western populations and are a heterogenous group of mature T-cell neoplasms arising from postthymic T cells at various stages of differentiation. NK-cell lymphomas are included in this group because of the close relationship between these 2 cell types. The importance of the T-cell phenotype and the impact on prognosis are now well established but are relatively recent advances. A large retrospective study, the International T-Cell Lymphoma Project (ITLP), collected 1153 cases of PTCLs from 22 centers from around the world and highlighted the geographic, clinicopathologic, and prognostic differences of this diverse group of diseases. There is a range of diseases among T- and NK-cell neoplasms, with most diseases behaving aggressively; however, a minority have a favorable prognosis or an indolent course (Table 23-1).

CLINICAL CASE

A 58-year-old White man with no significant medical history was noted to have generalized skin rash and itching with diffuse lymphadenopathy. He had drenching night sweats, extreme fatigue, and 20 lb (~9 kg) weight loss over the last 3 months. His complete blood count revealed an Hemoglobin of 8 g/L and a platelet count of 110×10^3/dL. His CTs of chest, abdomen, and pelvis showed diffuse lymphadenopathy and hepatosplenomegaly. He underwent left axillary lymph node excisional biopsy that showed total effacement of lymph node with CD4- and CD3-positive T cells. The neoplastic cells also express CD10, CD21, and PD1.

Aggressive PTCLs

Adult T-cell leukemia/lymphoma

Adult T-cell lymphoma/leukemia (ATLL) is a highly aggressive T-cell neoplasm that occurs in areas where infection with human T-lymphotropic virus 1 (HTLV-1) is endemic (eg, the Caribbean basin and southwestern Japan). ATLL typically follows decades-long asymptomatic chronic infection with HTLV-1. The cumulative incidence of ATLL among HTLV-1 carriers is 2.5% in Japan. The virus can be transmitted in breast milk and blood products. The malignant cells have a distinct cloverleaf appearance and are $CD7^-$, and most are $CD4^+/CD8^-$ and $CD25^+$. Four clinical variants have been recognized: (1) acute type with a rapidly progressive clinical course, including bone marrow and peripheral blood involvement, hypercalcemia with or without lytic bone lesions, skin rash, generalized lymphadenopathy, hepatosplenomegaly, and pulmonary infiltrates; (2) lymphoma type with prominent adenopathy, lacking peripheral blood involvement, but also associated with an aggressive course; (3) chronic type with lymphocytosis and occasionally associated with lymphadenopathy,

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hepatosplenomegaly, and cutaneous lesions, but having an indolent course; and (4) smoldering type with <5% circulating neoplastic cells, skin involvement, and prolonged survival. The chronic and smoldering forms can progress to the acute form after a variable length of time. In the ITLP, 126 patients (9.6% of all PTCLs) were identified with the acute (13%) or lymphoma-type (87%) ATLL. Opportunistic infections such as *Pneumocystis jirovecii* infection, fungal infections (*Candida*, *Aspergillus,* etc.), strongyloidiasis, and viral infections are common. Appropriate prophylactic antimicrobials are highly recommended before starting the therapy.

Survival times in the acute and lymphomatous variants are ~6 and ~10 months, respectively. The median survival for the chronic form is 2 years. The 4-year OS for the acute, lymphoma, chronic, and smoldering types has been reported to be 5%, 5.7%, 27%, and 63%, respectively. Asymptomatic patients with the smoldering or chronic-type ATLL can be monitored closely. For young, fit patients with the acute and lymphoma subtypes, the intensive CTH regimen incorporating VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisolone)/AMP (doxorubicin, ranimustine, and prednisolone)/VECP (vindesine, etoposide, carboplatin, and prednisolone) may be considered. The Japan Clinical Oncology Group (JCOG) reported a phase 3 trial comparing the dose-intensive regimen VCAP/AMP/VECP versus CHOP-14 alone that showed a more favorable CR rate (40% versus 25%, $P = 0.02$) and 3-year OS (24% versus 13%) that was significant after adjusting for prognostic factors but only for the one-sided P value ($P = 0.028$). The median survival for the intensive regimen was just over 1 year, but toxicity was high (grade 4 neutropenia in 98% and grade 3/4 infections in 32%). Thus, this regimen should be used only in carefully selected patients, particularly with the lymphoma subtype. As some of the chemotherapies are not available outside Japan, CHOP, CHOP with etoposide, or DA-EPOCH are commonly used alternatives. CNS disease occurs in 10% to 20% of aggressive ATLL patients and high-dose methotrexate (3 g/m^2) or intrathecal CTH must be incorporated in the treatment of ATLL.

A number of phase 2 studies evaluating the use of the antiretroviral zidovudine and IFN in untreated patients have found response rates up to 92% and a median OS of 11 months. For patients with the leukemia subtype, these results are superior to what is achieved with combination CTH, though the benefit appears minimal in the lymphoma subtype. For the patients with the chronic and smoldering types, a meta-analysis demonstrated 100% OS after 10 years with this approach.

The chemokine receptor 4 (CCR4) is expressed in ~90% of cases of the ATLL. Mogamulizumab (KW-0761) is a humanized monoclonal antibody targeting the CCR4; a phase 2 study demonstrated an ORR of 50%, including 8 CRs, in 27 treated patients. The median PFS and OS were 5.2 months and 13.7 months, respectively. The most common side effects were lymphopenia (96%), neutropenia (52%), thrombocytopenia (52%), infusion reaction (89%), and skin rashes (63%). Steroid-refractory GVHD has been reported in patients who had pretransplant mogamulizumab. Mogamulizumab is not FDA-approved for ATLL in the United States. In the ECHELON-2 study, which incorporated Brentuximab Vedotin (BV) with cyclophosphamide, doxorubicin and prednisone (CHP) in newly diagnosed CD30$^+$ PTCL, 7 patients were enrolled with ATLL. About 1/3 of ATLL cases express CD30. In the absence of real-world data, BV-CHP should be considered in newly diagnosed ATLL patients who expresses CD30 (>10%). As relapse rates are high in aggressive ATLL, patients who are fit and who have a suitable donor should undergo allogeneic stem cell transplantation.

Peripheral T-cell lymphoma

The revised WHO 2017 classification for the lymphoid malignancies identifies more than 30 distinct T- and NK-cell neoplasms. Apart from pathological and clinical diversity, the peripheral T- and NK-cell neoplasm have geographical variations. In North America, PTCL-NOS, angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large-cell lymphoma (ALCL, anaplastic lymphoma kinase [ALK]-negative and -positive) are common subtypes. In Asia, PTCL/NK-T-cell lymphoma associated with EBV and HTLV are common subtypes. Unfortunately, the aggressive T/NK-cell lymphomas have inferior overall survival, ranging from 9% to 35% at 5-years.

PTCL-NOS

PTCL-NOS is the most common subgroup of PTCLs, accounting for up to 30% to 35% of cases in North America. PTCL-NOS is the default PTCL category for any mature T-cell neoplasm that does not fit into any of the specified categories of the mature T-cell lymphomas in the WHO classification. Patients typically present with advanced-stage disease with rare paraneoplastic phenomenon like pruritus, eosinophilia, or Hemophagocytic lymphohistiocytosis. The 5-year OS is 20% to 30% in most series. Typically, the neoplastic cells are CD4$^+$/CD8; CD5 and CD7 frequently are lost; and 30% to 50% are CD30$^+$. Gene expression profiling studies have identified 2 main subgroups of PTCL-NOS, TBX21, and GATA3 expressing. The subgroup overexpressing TBX21 is associated with longer overall survival.

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The treatment approaches in PTCL parallel those for DLBCL; as a result, CHOP-like therapy (CHOP with etoposide [EPOCH]) is routinely employed as frontline therapy. The CD30 expression is important to identify for treatment of PTCL. BV with CHP should be considered in patients with higher (>10%) CD30 expressing PTCL. The DSHNHL group retrospectively analyzed the outcome of PTCL patients (n = 331) that had been enrolled in phase 2 or phase 3 aggressive lymphoma studies and evaluated the impact of etoposide. In patients younger than 60 years with a normal LDH, EFS was extended with etoposide (P = 0.003), whereas OS did not improve significantly (P = 0.176). The addition of etoposide appeared to have the greatest impact in the favorable group of patients with ALK-positive ALCL (3-year EFS 91% versus 82%, P = 0.012). In patients with PTCL-NOS, ALK-negative ALCL, and AITL, there was a trend toward improved 3-year EFS (61% versus 48%; P = 0.057), with no difference in OS; however, patient numbers were small. On the basis of these data, CHOEP may be considered as an initial therapy in younger patients. For sufficiently young and fit patients, upfront consolidation with HDC/ASCT is generally considered (see the section "Transplantation in PTCL" that follows).

About 75% of PTCL-NOS cases relapse after initial treatment. Pralatrexate, romidepsin, and belinostat are FDA-approved for relapsed PTCL-NOS. Unfortunately, the response rates and PFS remain inferior with these agents. Pralatrexate is a novel folate analogue that has enhanced uptake and cellular retention compared with MTX. Early studies suggested a sensitivity of TCLs over BCLs. The phase 2 PROPEL study evaluated pralatrexate in relapsed/refractory PTCLs and demonstrated an ORR 29% (CR 11%), a median PFS of 3.5 months, and a median DOR of 10.5 months. The main toxicities were mucositis, thrombocytopenia, and neutropenia. These results led to the FDA approval of pralatrexate in September 2009 for the treatment of relapsed/refractory PTCL. Studies combining pralatrexate with other agents in the upfront (with CHOP) and relapsed settings are ongoing.

Romidepsin is an Histone deacetylase (HDAC) inhibitor that has been evaluated in CTCLs and PTCLs. A phase 2B registration study evaluated romidepsin in 130 patients with relapsed or refractory PTCL. The ORR was 25% (CR 15%), median DOR was 28 months, and median PFS was 29 months, leading to the FDA approval in 2011. The final analysis of the Phase 3 study, adding romidepsin to CHOP in newly diagnosed PTCL, did not show improvement in the PFS and increased treatment-related toxicities.

Belinostat is another HDAC inhibitor that has demonstrated responses in the relapsed or refractory PTCL in a phase 2 trial. Belinostat was granted approval by the FDA for the treatment of patients with PTCL who have received at least one prior therapy. A phase 2 trial (BELIEF trial) of belinostat in 120 patients with PTCL reported overall and complete remission rates of 26% and 11%, respectively, with a median DOR of 13.6 months.

CD30 is an attractive therapeutic target. It is intensely and diffusely expressed in ALCL. In the other T-cell lymphomas, its expression is variable. BV was evaluated in relapse/refractory CD30+ (any expression) PTCL (PTCL-NOS: 22, AITL: 13, BV naïve). In CD30+ PTCL, ORR was 33% and CR was 14%. The PFS in PTCL-NOS patients was 7.6 months. In CD30+ AITL, ORR was 54% and CR was 24%. In AITL, the median PFS was 5.5 months. BV is an attractive treatment option for the relapse/refractory T-cell lymphoma with CD30 positivity. The expression (%) of CD30 positivity is still not well-defined for therapeutic efficacy of BV. Duvelisib, a dual delta and gamma PI3K inhibitor, has shown impressive activity in PTCL. In phase 2 study of duvelisib in R/R PTCL (PRIMO trial), ORR was 40% and CRR was 30%.

Angioimmunoblastic T-cell lymphoma and PTCL with T follicular helper (TFH) cell origin

AITL is a well-defined, distinct PTCL subtype with unique pathobiologic features. AITL has TFH cell gene expression signature and TFH cell–associated markers. The key morphologic findings of AITL include an expanded $CD21^+$ follicular dendritic-cell network and prominent arborizing high-endothelial venules. The neoplastic cells in AITL are mature $CD4^+/CD8^-$ T cells, expressing most pan-T-cell antigens. These cells also express TFH cell–associated markers like CD10, CXCL13, *BCL6*, CXCR5, etc. Follicular T-cell lymphoma and nodal PTCL with T follicular helper phenotype are TFH cell–origin T-cell lymphomas. Their clinical course overlaps with AITL, but differ from AITL pathobiologically. These subtypes of PTCL have higher degree of epigenetic dysregulation. Sequencing studies have shown this PTCL subtype to be enriched for mutations of *TET2*, *IDH2*, *DNMT3A*, *RHOA*, and *CD28*.

Patients are typically in their sixth or seventh decade and have advanced-stage disease, often with B symptoms and hepatosplenomegaly. Interestingly, these patients may have skin rashes and autoimmune phenomena (hemolysis, Immune Thrombocytopenia, or Evans syndrome).

Survival is similar to that in PTCL-NOS (5 year, ~30%); however, a small proportion of patients may have a more indolent course. CHOP or CHOEP is typically used as primary therapy and, although the response rate is high, relapse is common and infectious complications are

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problematic. GELA evaluated AITL patients enrolled in different therapeutic protocols and found no improvement of survival with any therapy, including HDC/ASCT.

Because of poor outcomes using conventional therapy, immunomodulatory agents, including cyclosporine, lenalidomide, thalidomide, and interferon, also have been explored. A retrospective study evaluating cyclosporine in relapsed or refractory AITL demonstrated an ORR of 67% and a median DOR of 13 months. Because of epigenetic dysregulation, HDAC inhibitors have shown higher activity in AITL and TFH T-cell lymphomas compared to the other T-cell lymphomas. Romidepsin and belinostat had ORRs of 30% and 45%, respectively in AITL in their pivotal studies. 5-Azacytidine showed an impressive ORR of 75% (CRR 42%) in a small study. In another study, romidepsin and 5-azacytidine showed an ORR of 83% and a CRR of 50% in AITL. Similarly, brentuximab vedotin has produced encouraging response rates in relapsed AITL, where the infiltrating B immunoblasts are usually $CD30^+$.

Follicular T-cell lymphoma and nodal PTCL with TFH phenotype are also distinct nodal T-cell lymphomas derived from the same TFH cell as AITL. They share recurrent genetic abnormalities with AITL, including *TET2*, *IDH2*, *DNMT3A*, *RHOA*, and *CD28* mutations as well as t(5;9) *ITK-SYK* fusion. The clinical course of these rarer variants is not yet well-characterized, but they appear to have an aggressive clinical course similar to AITL.

Systemic anaplastic large-cell lymphoma

ALCL is composed of large $CD30^+$anaplastic cells with a predilection for a sinusoidal and cohesive growth pattern. ALCL are classified into 3 categories: systemic ALCL, primary cutaneous ALCL, and breast implant-associated ALCL. Systemic ALCL cases are divided into 2 groups: ALK positive and ALK negative (Table 23-1). Cases of ALK-positive ALCL are associated with a characteristic chromosomal translocation, t(2;5)(p23;q35), resulting in a fusion gene, *NPM-ALK*, encoding a chimeric protein with tyrosine kinase activity. With the availability of antibodies to the ALK protein, ALK expression can be demonstrated in 60% to 85% of all systemic ALCL, with higher frequencies seen in the pediatric and young adult age groups.

ALK-positive ALCL

Morphologically, ALK-positive ALCL has the pathognomonic hallmark cells, recognized by their eccentric, horseshoe, or kidney-shaped nuclei with abundant cytoplasm. In addition to strong expression of CD30, ALK-positive ALCL is usually positive for epithelial membrane antigen and cytotoxic markers (TIA1, granzyme B, and perforin). Several studies have established that patients with ALK-positive ALCL have a more favorable prognosis with anthracycline-based CTH than patients who have ALK-negative ALCL (5-year OS ~80% versus ~45%). The improved outcome, at least in part, is related to the young age and low-risk features often present at presentation. The ITLP and other retrospective analysis also showed no effect of ALK status on PFS or OS in younger (<40 years old) patients.

Given the favorable outcome with the anthracycline-based CTH, CHOP-like therapy is considered the standard therapy for ALK-positive ALCL. A subset analysis of ALK-positive ALCL patients treated in prospective studies from the German High-Grade Lymphoma Study Group has identified a particularly favorable outcome among patients treated with CHOEP (3-year EFS, 92%). More recently, the ECHELON-2 study, a randomized phase 3 trial evaluated the upfront addition of BV to CHP compared to the standard CHOP in $CD30^+$ T-cell lymphomas (70% were ALCL). A total of 452 patients were randomized, and the study found an improved PFS favoring the BV-CHP arm (hazard ratio 0.71, $P = 0.01$). Overall survival was similarly improved among BV-CHP–treated patients (hazard ratio 0.66, $P = 0.024$). Based on these data, BV-CHP can now be considered standard frontline therapy for ALK^+ or ALK^- ALCL.

Crizotinib and other small-molecule inhibitors of the ALK tyrosine kinase, FDA-approved for treatment of ALK-positive non–small-cell lung cancer, have also demonstrated remarkable clinical activity in patients with multiply relapsed ALK-positive ALCL and may be considered in patients with disease that has been refractory to both CTH and brentuximab vedotin.

ALK-negative ALCL

Patients with ALK-negative ALCL tend to be older at presentation; the clinical presentation is similar to PTCL-NOS, but sites of extranodal disease may vary. Histologically, ALK-negative ALCL is not reproducibly distinguished from the common pattern of ALK-positive ALCL except that it lacks the ALK protein. Important differential considerations are primary cutaneous ALCL, other B- or T-cell $CD30^+$ lymphomas with anaplastic features, and cHL. Prognostically, ALK-negative ALCL falls between ALK+ ALCL and PTCL-NOS. Gene expression studies have shown that ALK-negative ALCL has a signature distinctly different from PTCL-NOS and similar to that of ALK-positive ALCL. A subset of ALK-negative ALCL cases carry *DUSP22-IRF4* rearrangements and

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appear to have superior outcomes, similar to that of ALK-positive ALCL, while another subset carrying *TP63* rearrangements have poor outcomes. These data confirm that ALK-negative ALCL should be considered distinct from both the ALK-positive ALCL and PTCL-NOS. Although the survival for ALK-negative ALCL is more favorable than for PTCL-NOS, it is still poorer than for ALK-positive patients, except in patients carrying the *DUSP22-IRF4* rearrangement.

BV-CHP is a very effective regimen for ALCL based on the ECHELON-2 trial, as described previously. Upfront consolidation with HDC/ASCT is generally considered for ALK-negative patients, particularly those lacking the *DUSP22-IRF4* rearrangement (see the section on transplantation, which follows). Brentuximab vedotin is highly effective in the relapsed/refractory setting if not already incorporated with frontline therapy. A phase 2 study, reported in relapsed or refractory systemic ALCL (BV-naïve), demonstrated an ORR of 86% (CR 57%), median DOR of 12.6 months, and a median PFS of 13.3 months, which prompted the FDA approval of brentuximab vedotin for R/R ALCL in 2011. The main side effect of brentuximab vedotin is peripheral neuropathy.

Breast implant-associated ALCL

Morphologically and immunophenotypically similar to ALK-negative ALCL, this type of ALCL arises in the setting of prior breast implants. It typically presents as an unexplained seroma or capsule thickening. The lymphoma typically involves the capsule of implants without invasion of the breast tissue or formation of discrete mass lesions. Almost all cases are localized. The neoplastic cells float in the effusion fluid or become embedded in tissue and infiltrate the cavity containing the implant. The breast implant-associated ALCL has been associated with both silicone and saline implants but, importantly, it occurs almost exclusively in implants with a textured surface. The preferred and effective treatment is surgical total capsulectomy. Removal of the uninvolved breast implant on the opposite side is highly recommended. The growing body of literature supports that ALK-negative ALCL in this setting appears to have an indolent clinical course with a favorable prognosis, and most patients can be observed following removal of the implant and capsule without adjuvant CTH. Some reports suggest similar survival rates compared with those who received CTH or radiation; however, rare aggressive cases have been reported. In locally advanced unresectable and systemic cases, CTH may benefit. Cases that have identified a distinct breast mass may be better classified as a typical systemic ALK-negative ALCL and may be treated accordingly.

Extranodal NK-/T-cell lymphoma, nasal type

Extranodal NK-/T-cell lymphoma, nasal type, displays great variation in racial and geographic distribution, with the majority of cases occurring in Asia. This lymphoma is characterized by angioinvasion, necrosis, cytotoxicity, and association with EBV. The designation NK-/T is used to reflect the fact that, although most cells are NK-cell derived ($CD2^+$, $CD56^+$, CD3 [cytoplasmic]$^+$, EBV-positive), some cases with identical clinical and cytologic features exhibit an EBV-positive or $CD56^-$, cytotoxic T-cell lineage (TIA1, perforin, and granzyme B). The circulating EBV in the peripheral blood can often be detected, providing another method of disease monitoring. Patients are typically males aged 40 to 50 years. Most cases remain localized but may be extensively locally invasive, with <20% of patients presenting with advanced-stage disease. Despite the predominant nasal location, spread to the CSF is uncommon. Most occur in the nasal region, but identical tumors also can occur at extranasal sites, such as skin, soft tissue, GI tract, and testis. The cases involving extranasal regions may have a more aggressive course. From the ITLP, the 5-year OS for stage I/II NK-/T-cell lymphomas were ~50% and 15% for nasal and extranasal sites, respectively, and the corresponding estimates for stage III/IV patients were 30% and <10%. The IPI does not stratify patients well because most have localized disease and often with good PS. A Korean index, using B symptoms, stage (I/II versus III/IV), regional lymph nodes, LDH, and PS, appears to be more useful in prognostication, particularly for the low- and low-intermediate IPI cases and may help to guide treatment decisions. The patients fall into 4 risk groups with widely disparate outcomes: group 1, no risk factors (RFs), 5-year OS ~ 81%; group 2, 1 RF, 5-year OS ~64%; group 3, 2 RFs, 5-year OS ~34%; and group 4, 3 or 4 RFs, 5-year OS 7%. Risk factors identified in other studies have also included local tumor invasion (bone or skin), high Ki-67, or EBV DNA titer $>6.1 \times 10^7$ copies/mL. Unfortunately, the NK-/T-cell lymphoma is aggressive, with historic median survival less than 2 years.

Limited stage, I to IIE, is usually restricted to a single radiation field. There are 3 approaches to treat limited-stage disease: (1) sequential therapy with CTH followed by consolidative radiation, including a "sandwich" approach; (2) concurrent radiation and CTH; and (3) radiation therapy alone in selected cases. Radiation is an essential component of NK-/T-cell lymphoma. The recommended dose of radiation is more than 50 Gy, as it is associated with improved survival. A radiation dose of 40 to 54 Gy may be selected with concurrent intensive CTH. One meta-analysis showed survival

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advantage with radiation first followed by CTH without any impact of CTH regimens or radiation dose. Sequential or concurrent CTH with radiation therapy is reasonable approaches for early-stage NK-/T-cell lymphoma. Use of platinum-based concurrent CTH as a radiosensitizer appears highly effective. Furthermore, because systemic relapse can occur with single-modality radiotherapy, other novel combinations are being tested. The outcome with CHOP has been disappointing, and it has been speculated that this may be caused by the overexpression of p-glycoprotein expression conferring multidrug resistance. Concurrent radiation (40 Gy) and cisplatin, followed by 3 cycles of etoposide, ifosfamide, cisplatin (VIPD), was evaluated in stage IE/IIE nasal NK-/T-cell lymphoma. In this highly selected population, the CR rate was 83% and the 3-year PFS was 85%. Similarly, concurrent radiotherapy (50 Gy) and DeVIC CTH (dexamethasone, etoposide, ifosfamide, carboplatin) was evaluated with good results in a phase 1/2 trial in localized nasal NK-/T-cell lymphoma (CR 77%, 2-year PFS 67%). The sandwich approach, with LVP (L-asparaginase, vincristine and prednisone), LVDP (L-asparaginase, cisplatin, etoposide and dexamethasone) and L-GemOx (L-asparaginase, gemcitabine and oxaliplatin), has shown encouraging results in early-stage NK-/T-cell lymphoma.

Unfortunately, 20% to 30% of patients with NK-/T-cell lymphoma present with advanced-stage disease. Their prognosis is extremely poor, with median survival ranging from 4 to 7 months. For advanced-stage disease, asparaginase-containing regimens have shown superior activity. Adding asparaginase has shown improved ORR, CR, and median survival. A phase 2 study that evaluated L-asparaginase in combination with MTX and dexamethasone (AspaMetDex) in previously treated patients demonstrated an ORR of 78% (CR 61%) and a median DOR of 12 months. A phase 2 study evaluating the SMILE regimen (steroid, methotrexate, ifosfamide, L-asparaginase, etoposide) in 38 patients with newly diagnosed stage IV or relapsed or refractory NK-/T-cell lymphoma demonstrated an ORR after 2 cycles of 79% (CR 45%); 19 patients subsequently underwent SCT. The 1-year OS rate was 55%, but grade 4 neutropenia occurred in 92% and the grade 3/4 infection rate was 61%. For patients with advanced-stage disease who are sufficiently young and fit for intensive therapy, SMILE has emerged as preferred therapy. DDGP (cisplatin, dexamethasone, gemcitabine and peg-asparaginase), P-GemOx (peg-asparaginase, gemcitabine, and oxaliplatin) and AspaMetDex are less-toxic alternatives to the SMILE regimen. ASCT has been used as consolidative strategy with highest benefit in advanced-stage high-risk patients in CR1. In select patients with the advanced-stage disease in CR1, allogeneic SCT could be curative. For patients with relapsed/refractory disease, PD-1 inhibition with pembrolizumab and CD38 directed daratumumab have shown encouraging activity that warrants further exploration.

Aggressive NK-cell leukemia

Aggressive NK-cell leukemia is a rare form of leukemia that almost always is associated with EBV infection and has a median survival of only 3 months. It is seen most often in Asians, and the median age of onset is 42 years. Typically, the patients present with acute illness with fever, constitutional symptoms, multiorgan failure, Disseminated Intravascular Coagulopathy, and hemophagocytic syndrome. Commonly, liver, spleen, bone marrow, and peripheral blood are involved with malignant NK/T cells. EBV viremia is commonly seen in these patients. It is unclear whether the aggressive NK-cell leukemia represents the leukemic phase of extranodal NK-/T-cell lymphoma. There is no known curative therapy, and responses to CTH are usually brief. Some patients may benefit with asparaginase based intensive induction CTH (as detailed in the preceding section on NK-/T-cell lymphoma) followed by allo-SCT.

Uncommon aggressive PTCL subtypes

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL) is a rare form of primary cutaneous lymphoma of αβ T cells infiltrating subcutaneous tissue like panniculitis. It has been determined that tumors with the γδ phenotype have a far inferior prognosis compared to those with the αβ phenotype (5-year OS, 11% for γδ versus 82% for αβ). In the WHO classification, SCPTCL is confined only to αβ T cells, which usually have a $CD4^-/CD8^+$ and $CD5^-$ phenotype. The γδ phenotype is included separately as *primary cutaneous γδ T-cell lymphoma* (see the section "Primary cutaneous PTCL, rare aggressive subtypes") because of its more aggressive behavior. Autoimmune diseases occur in 20% of cases and remain the main differential diagnoses. Most SCPTCL has an indolent clinical course and overall good prognosis. In about 20% of cases, it may have an aggressive course with hemophagocytic syndrome. Optimal therapy for αβ-type SCPTCL is unknown, with durable responses observed with CHOP-based therapy. An aggressive approach with ASCT has shown benefit in patients with hemophagocytic syndrome. In relapsed cases, cyclosporine, methotrexate, and steroids have shown reasonable activity. Radiation therapy could be included for localized disease.

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Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma is a rare and very aggressive PTCL subtype occurring usually in young men (median age 34 years) presenting with hepatosplenomegaly and bone marrow involvement. Up to 20% of hepatosplenic T-cell lymphomas occur in the setting of immunosuppression, most commonly following solid-organ transplantation, and may occur a decade or longer after transplantation. In this setting, it is considered PTLD. It has been observed in patients with chronic immunosuppression with thiopurines or in combination with TNFα inhibitor in inflammatory bowel disease. Usually, small, medium-sized γδ T cells demonstrate sinusoidal infiltration of spleen, liver, and bone marrow. Most tumor cells are $CD3^+$, $CD4^-$, and $CD8^-$, and most are associated with isochromosome 7q. The majority of cases are of the γδ TCR type; however, rare cases of the αβ TCR type have been reported. The prognosis is extremely poor and long-term survival is rare. The optimal therapy is unknown; however, CHOP seems inferior. High-dose cytarabine-based strategies, such as with IVAC, have been reported to be more effective in case reports. Long-term survivors have been reported with allo-SCT, and early referral for transplantation at diagnosis is suggested.

Enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic intestinal T-cell lymphoma

Recent findings have led to changes in the categorization of intestinal T-cell lymphomas. The 2 previously described variants of the enteropathy-associated T-cell lymphoma (EATL) are now recognized as distinct; what was previously type II EATL is now designated as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). Type I EATL is designated as EATL. EATL is a rare, aggressive intestinal tumor with a male predominance that often occurs in the setting of celiac disease and typically in patients of Northern European heritage. In contrast, MEITL shows no association with celiac disease and tends to occur in Asian and Hispanic populations. Both diseases commonly involve the jejunum or ileum with patients often presenting with abdominal pain; intestinal perforation can occur. The prognosis is extremely poor because of CTH resistance and the difficulty of treatment delivery because of abdominal complications that can arise in the setting of malabsorption. In EATL, the neoplastic cells are typically polymorphous $CD3^+$, $CD7^+$, $CD4^-$, $CD8^{-/+}$, $CD56^-$αβ T cells. In contrast, the neoplastic cells in MEITL are typically monomorphic $CD3^+$, $CD4^-$, $CD8^+$, and $CD56^+$ γδ T cells.

The ITLP reported on 62 patients with intestinal T-cell lymphoma, which represented 5.4% of all lymphomas worldwide, occurring most commonly in Europe. EATL and MEITL represented 66% and 34% of cases, respectively. The 5-year FFS was only 4% and OS was 20%, with the majority of patients treated with CHOP-type CTH. Similar disappointing results are observed in other studies with CHOP-type therapy, which has prompted evaluation of HDC/ASCT (see the section "Transplantation in PTCL").

Primary cutaneous PTCL, rare aggressive subtypes

Primary cutaneous γδ T-cell lymphoma

In the updated WHO classification, primary cutaneous γδ T-cell lymphoma is now considered a distinct entity, which also includes cases previously known as SCPTCL with a γδ phenotype, as described earlier. Clinically, the extremities are commonly affected, and the presentation can be variable, with patch or plaque disease or subcutaneous and deep dermal tumors that may exhibit necrosis and ulceration. The clonal T cells have an activated γδ cytotoxic phenotype and most are $CD4^-/CD8^-$. Prognosis is poor in this disease, particularly with subcutaneous fat involvement, with a fulminant clinical course and chemoresistance.

Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma

This provisional entity typically presents with generalized cutaneous lesions appearing as eruptive papules, nodules, and tumors with central ulceration and necrosis. Histologically, there is marked epidermotropism, and invasion into the dermis and adnexal structures is common. The tumor cells are $CD3^+$, $CD4^-$, $CD8^+$, and cytotoxic marker–positive, and the clinical course is aggressive.

Transplantation in PTCL

Multiple retrospective studies have been published evaluating the impact of upfront transplantation in PTCL. Trial interpretation and comparisons are difficult for several reasons, including the evaluation of heterogeneous patient populations, potential for selection bias, and the dearth of intention-to-treat data. Because there are no reported prospective randomized phase 3 trials comparing HDC/ASCT with conventional-dose CTH specifically for PTCL, it remains challenging to determine the relative impact of patient selection versus true differences in efficacy.

Several phase 2 prospective studies of upfront transplantation have been published and represent more homogeneous populations of treated patients. The Nordic

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Lymphoma Study Group completed the largest prospective phase 2 trial of upfront transplantation (NLGT-01) in 160 patients with PTCL, excluding ALK-positive ALCL. The planned treatment scheduled was CHOEP-14 for 6 cycles (CHOP-14 in patients >60 years old), followed by BEAM/BEAC and ASCT in responding patients. In this patient population, the pretransplant CR rate was 81% with 70% transplant rate and 4% TRM. With a median follow-up of 5 years, the 5-year PFS was 44% and the 5-year OS was 51%. Patients with ALK-negative ALCL appeared to have a superior 5-year PFS (61%) compared with PTCL-NOS (38%), EATL (38%), or AITL (49%), but these results were not statistically significant. The 5-year OS for patients who underwent transplantation was 61% compared with 28% in those who did not. Combined results of 2 prospective phase 2 studies investigating role of upfront transplant in advanced treatment-naïve PTCL, at a median follow-up of 76 months, estimated 12-year OS and PFS were 35% and 55% respectively. In this report, ALK-positive group had the best outcome (OS 62% versus 21%, $P = 0.005$). Multivariate analysis of these studies showed that pretransplant CR rates had OS and EFS benefit.

For relapsed/refractory patients, HDC/ASCT represents the standard of care for eligible patients who have not undergone upfront transplant consolidation. In the original Parma study, in which HDC/ASCT emerged as superior to second-line CTH alone in relapsed aggressive NHL, immunophenotyping was not routinely performed. A subsequent report of prognostic factors did not identify a difference in outcome in B- versus T-cell lymphomas; however, the number of patients with PTCL was small. There has been no similar randomized study in PTCLs, but several retrospective studies report a salvage rate in this setting ranging from 18% to 60%. Given the overall body of evidence, ASCT frequently is offered to patients with PTCL with relapsed, chemosensitive disease.

Allo-SCT, with myeloablative or RIC, also has been reported to yield durable remission in many cases (3-year EFS, 23% to 64%). Evidence supporting a graft-versus-PTCL effect comes from studies with donor lymphocyte infusions. The largest study published to date evaluated 77 previously treated patients with mainly myeloablative conditioning (74%). The 5-year PFS was 53%, but the TRM was 34% at 5 years. A phase 2 trial, evaluating RIC and allo-SCT in 17 patients, demonstrated a 3-year PFS of 64% with a TRM of 6%. Allogeneic transplantation is promising in the treatment of PTCL, but it is limited by the availability of stem cell donors and by toxicity related to GVHD.

KEY POINTS

- *TP53*-mutated MCL is a distinctively aggressive subtype associated with blastoid morphology, high proliferative index, high-risk MIPI score, and resistance to intensive induction therapy.
- High HIV viral load and low CD4 count (<50/μL) are associated with increased toxicity with CTH in HIV-related lymphomas.
- Patients with congenital or acquired immunodeficiency have an increased risk of lymphoma and often respond poorly to therapy.
- PTCLs have an outcome inferior to that of DLBCL. The exceptions are ALK-positive ALCL and ALK-negative ALCL with DUSP22-IRF4 rearrangements, which have a high cure rate with CHOP, CHOEP, or BV-CHP CTH.

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